EPIDEMIOLOGIC APPROACHES TO UNDERSTANDING GONORRHEA TRANSMISSION DYNAMICS AND THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

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ABSTRACT

Globally, the incidence of infection caused by *Neisseria gonorrhoeae* is the second highest among the bacterial sexually transmitted infections. In Canada, declining rates during the 1990s suggested progress toward curbing gonorrhea; however, those have been increasing since 1999, with rates in Saskatchewan among the highest in the country. Infection can cause serious complications in men and women, and reported resistance to third-generation cephalosporins could lead to potentially untreatable infections. Increased understanding of gonorrhea transmission dynamics, sexual networks, and predictors of antimicrobial resistance development is needed to inform the development of improved approaches to prevention and treatment.

The research presented herein draws upon data from Shanghai, China, and Saskatchewan, Canada, to compare and contrast varying epidemiologic approaches to enhancing understanding of gonorrhea in the two settings. Using traditional statistical approaches, multi-level statistical modeling, social network analysis, and dynamic simulation modeling, questions related to sexual behavior, partner presentation, and antimicrobial resistance development are explored. Each technique is evaluated for its potential contribution to overall understanding of the issues related to the ongoing gonorrhea epidemic, globally, and in Saskatchewan.

The relative strengths and limitations of the application of the analytical approaches in the different settings are described. Socio-demographic characteristics provided useful indicators of antimicrobial resistant infection among patients with gonorrhea from Shanghai. Further, socio-demographic characteristics were also useful for predicting presentation of a partner for testing and treatment and the use of condoms during intercourse, among this study population. In Saskatchewan, socio-demographic characteristics were useful in predicting coinfection with gonorrhea and chlamydia at the time of diagnosis as well as repeat infection with gonorrhea. Social network analysis of the Saskatchewan dataset provided little additional understanding of the gonorrhea epidemic in the province. This result was largely related to how STI data are collected and stored in the province. The utility of dynamic simulation modeling to investigate the potential impact of antimicrobial resistance in Saskatchewan was also limited due to the same data constraints. However, the insight gained from the model building process and findings from the working model did offer a starting point for conversations around the best ways to postpone

the development of antimicrobial resistance in *N. gonorrhoeae* in Saskatchewan, as well as contribute additional information about how the ways in which STI data are collected and stored in the province considerably restrict the applicability of otherwise powerful epidemiologic tools.

With persistently high rates of disease transmission, and the threat of untreatable infections due to antimicrobial resistance, *N. gonorrhoeae* remains a substantial public health threat locally and globally. The research presented herein describes various approaches to understanding and controlling this disease, applied in contrasting settings. There are a wide variety of elements that should be considered when choosing the appropriate tool(s) to address gonorrhea in a given population; there is no "one size fits all" solution. The local epidemiology of disease, cultural and behavioural norms, the characteristics of the notifiable disease reporting and information systems, and the availability of suitable data all affect the relative strengths and weaknesses of the available analytic methods and disease control approaches.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
AMR	antimicrobial resistance
BTI	brought-to-treatment index
CDC	United States Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CNDSS	Canadian Notifiable Disease Surveillance System
DGI	disseminated gonococcal infection
EPT	expedited partner therapy
GASP	Gonorrhoeae Antimicrobial Surveillance Program
GEE	generalized estimating equations
GLLMM	generalized linear mixed model
HIV	human immunodeficiency virus
HSN	health services number
ICC	intraclass correlation coefficient
iPHIS	Integrated Public Health Information Service
IQR	interquartile range
MIC	minimum inhibitory concentration
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NML	National Microbiology Laboratory
OR	odds ratio
PCR	polymerase chain reaction
PHAC	Public Health Agency of Canada
PID	pelvic inflammatory disease
PPNG	penicillinase producing *Neisseria gonorrhoeae* (plasmid-mediated resistance)
QRNG	quinolone resistant *Neisseria gonorrhoeae* (chromosomal resistance)
RQHR	Regina Qu'Appelle Health Region
SD	standard deviation
SDCL	Saskatchewan Disease Control Laboratory

SNA	social network analysis
SSTISDH	Shanghai Sexually Transmitted Infection and Skin Disease Hospital
STI	sexually transmitted infection
TRNG	tetracycline resistant *Neisseria gonorrhoeae* (plasmid-mediated resistance)
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Infections caused by *Neisseria gonorrhoeae* have plagued humankind since ancient times. Gonorrhea was likely known to the authors of the Bible, which describes gonorrhea-like symptoms in the book of Leviticus; extensive descriptions of the disease date back at least to the time of Hippocrates (460-377 BC). Galen (130-200 AD), a Greek physician, is credited with giving the disease its name, based on the Greek words for "flow of semen (1)." The etiologic agent wasn't discovered, however, until 1879, by Albert Neisser, a German physician (2).

N. gonorrhoeae is a gram negative bacterium that only infects humans. It is relatively fragile, and unable to survive long outside the human body. The organism is spread by close physical contact with an infected individual's mucosal surfaces, and is transmitted almost exclusively through sexual partnerships. Gonococcal infection causes localized infections of the eyes, mouth, throat, rectum, and/or urogenital tract of both males and females.

1.1 Clinical features of infection

1.1.1 Men

Urethral gonorrhea in men generally causes painful urination and/or urethral discharge, typically appearing two to five days after infection (3). In the absence of treatment, most cases of urethral infection will resolve over a period of several weeks (4). Potential complications for men include epididymitis (4), which may cause testicular or scrotal pain. In rare cases, epididymitis can lead to infertility in men. While less common among men than among women, many men experience asymptomatic gonorrhea (5), potentially increasing their chance of complications due to failure to seek treatment.

1.1.2 Women

Urogenital infections in women occur primarily in the endocervical canal, and are often asymptomatic. When symptoms do occur, they generally occur within 10 days of exposure. Symptoms may include painful urination, increased vaginal discharge, or mid-cycle vaginal bleeding (4). However, symptoms are generally mild and may be mistaken for other conditions such as bladder or vaginal infections (6). Even in asymptomatic infections, serious complications can occur as a result of gonococcal infection in women. If the infection spreads to the uterus or fallopian tubes, pelvic inflammatory disease (PID) may occur. PID can cause internal abscesses,

chronic pelvic plain, and damage to the fallopian tubes may result in infertility or increased risk of ectopic pregnancy (7).

Gonorrhea during pregnancy is of particular concern; an infected woman may pass the infection on to her baby during delivery. This can result in ophthalmic infection for the baby, possibly leading to blindness (8). Disseminated gonococcal infection (DGI) is another serious potential complication of gonorrhea in newborns, usually occurring within one to four weeks of birth (8).

1.1.3 Men and women

Rectal and pharyngeal infections can occur in both sexes, and are particularly common among men who have sex with men (MSM) (4). Rectal infection can be asymptomatic, or can present with discharge, soreness, bleeding, itching, and/or painful bowel movements (9). Pharyngeal infection is typically asymptomatic, but can cause a sore throat (10). In both men and women, untreated gonorrhea can lead to DGI, which is potentially life-threatening. Men and women diagnosed with gonorrhea are commonly coinfected with chlamydia as well (11,12). Additionally, studies have shown that infection with gonorrhea and other STIs enhances HIV transmission (13,14).

1.2 Gonorrhea control

In the absence of a vaccine to prevent infection, control of gonorrhea depends on a combination of rapid diagnosis, appropriate treatment, and case-finding/partner notification.

1.2.1 Diagnosis and treatment

Laboratory diagnosis relies upon the identification of *N. gonorrhoeae* isolates recovered from the site(s) of infection by examination of stained smears, by culture, or by genetic or immunochemical tests. Increasingly, non-culture methods are becoming the primary method of diagnosis in North America and Western Europe; however, culture remains the standard in many other locations (4). In Canada, laboratory testing to confirm diagnosis of gonorrhea is generally done using nucleic acid amplification tests (NAAT), which can be performed on urine samples. Although NAAT is less invasive and more convenient than taking swabs for culture, to date there is no established method of identifying antimicrobial resistance (AMR) in *N. gonorrhoeae* using NAAT or other non-invasive techniques. Therefore, cultures are recommended to enable effective surveillance of (AMR) trends (15,16). Additionally, the Public Health Agency of

Canada (PHAC) recommends that all suspected treatment failures be investigated using culture (17).

Because of increasing rates of AMR, treatment guidelines are continuously updated to ensure that the most effective available antibiotics are used. Resistance varies in different geographic areas of the world, and treatment guidelines are developed regionally. In China, national guidelines recommend the use of ceftriaxone (250 mg IM) and spectinomycin (2g IM); the cost of antibiotics is covered by public health (Dr. Weiming Gu, personal communication 2015). In Canada, dual therapy is recommended due to increasing rates of AMR, as well as to address concomitant chlamydia infection. At the time of writing, combination ceftriaxone (250 mg IM in a single dose) and azithromycin (1 g po in a single dose) OR cefixime (800 mg po in a single dose) and azithromycin (1 g po in a single dose) were recommended as the preferred treatment for anogenital and pharyngeal infection, along with repeat screening 6 months after treatment. A recent Canadian report shows that this combination therapy is more effective than monotherapy with oral cefixime (18). Directly observed therapy—where the treatment is administered during the clinical visit and observed by the clinician—is recommended for all cases, as is test of cure 3-7 days after treatment in certain cases (17). In Saskatchewan, approved antibiotics to treat bacterial STIs are provided to patients without cost (19).

1.2.2 Reporting and partner notification

Along with diagnosis and treatment, partner notification is an important aspect of disease control. Gonorrhea is a notifiable disease in many countries, including both China and Canada—the two geographic settings for the data analyzed and presented in this dissertation (20,21). This means that all laboratory-confirmed cases must be reported to the appropriate public health authorities to support monitoring and control efforts. In China, the National Center for STD Control, in Nanjing, is responsible for surveillance of STIs. Law requires that all new cases of gonorrhea are reported to this national surveillance system (20,22). In Canada, cases are reported to the Canadian Notifiable Disease Surveillance System (CNDSS), on a voluntary basis, by provincial public health authorities who are responsible for notifiable disease surveillance and follow up (21).

PHAC guidelines include case-finding and partner notification for all positive gonorrhea cases, with a trace-back period of 60 days. If needed, local public health authorities may assist in

partner notification and follow up. It is recommended that all sexual partners who are located are tested, and presumptively treated, regardless of the existence of signs and symptoms. Further, recommended follow up of all positive cases includes repeat testing 6 months after treatment. In certain circumstances—including pharyngeal infection, persistent signs and symptoms after treatment, re-exposure, and poor compliance, among others—test of cure is recommended 3-7 days (for culture) or 2-3 weeks (for NAAT) after initial treatment (17).

1.2.3 High risk groups

PHAC identifies several populations at risk for gonorrhea. These include contacts of a confirmed case, individuals who have had unprotected sex with a resident of an area with high rates of disease and/or high rates of AMR, individuals who have previously been infected with an STI (including HIV), sex workers and their partners, sexually active individuals under 25 years of age, the street-involved and homeless, MSM, and those with multiple sex partners (23). These groups may warrant heightened surveillance or specific, targeted interventions.

1.3 Epidemiology of gonorrhea

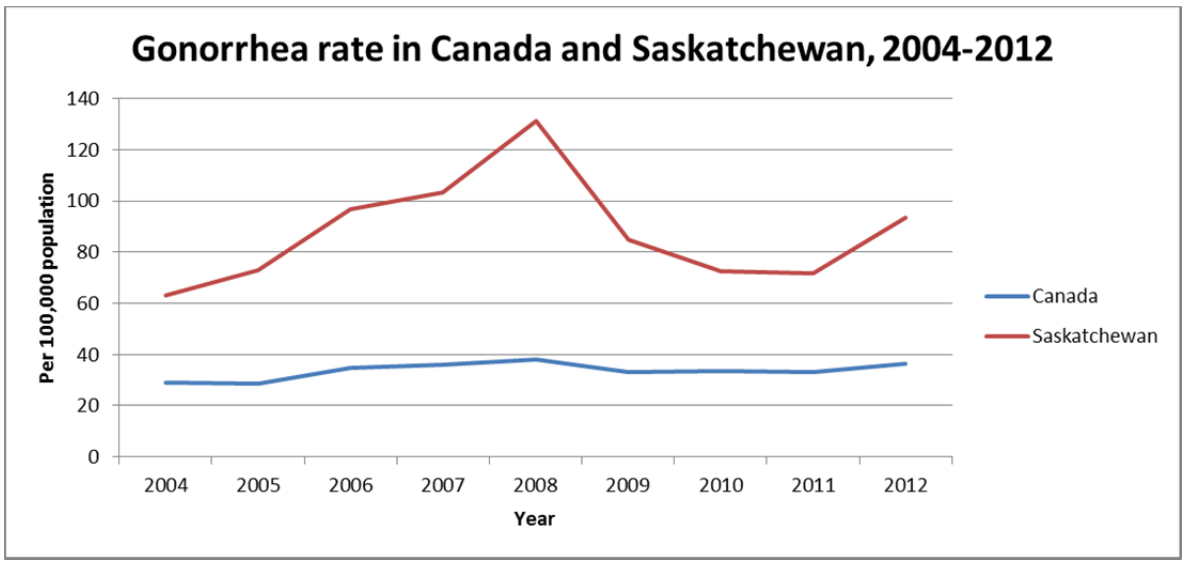
Globally, gonorrhea rates have been increasing. Incidence of gonorrhea is the second highest among the bacterial STIs, with an estimated 78 million new cases each year according to the most recent data from the World Health Organization (24). Because gonorrhea is often asymptomatic, it is possible that the true burden of disease is actually much higher. Rates of gonorrhea are typically highest among younger individuals. In the US, most infections are diagnosed among women 15-24 and men 20-24 (25), while in Canada, data indicate women 15-19 and men 20-24 exhibit the highest infection rates (17).

1.3.1 China

Rates of bacterial STIs, including gonorrhea, are high in China. After intensive control efforts led to a reduction in rates during the 1980s, subsequent social and economic changes have led to a rebound in rates since then. While incomplete reporting systems and lack of diagnostic capabilities in many regions limit the ability to estimate the true burden of disease (26), a national population-based study reported gonorrhea prevalence of 80 per 100,000 among women, and 20 per 100,000 among men (27). Rates of gonorrhea are especially high among high-risk subgroups of the population, including female sex workers and MSM (20,27).

1.3.2 Canada and Saskatchewan

Incidence of gonorrhea has been increasing in Canada since the 1990s, with a 38.9% increase between 2003 and 2012 (28). Gonorrhea is more common among young women than young men (age <25) in Canada, but the reverse is true for older age groups. In 2012, the Canadian national rate was 36.2 cases per 100,000. Saskatchewan's rate was 93.6 per 100,000—second only to Manitoba among the provinces, three times the rate of Ontario, Quebec, and British Columbia, and over twice the national rate (Figure 1.1) (28).



Data source: PHAC and iPHIS; modified from: http://communityview.ca/infographic_SHR_sti_2014.html

Figure 1.1 Gonorrhea in Canada and Saskatchewan, 2004-2012

1.4 Antimicrobial resistance in *N. gonorrhoeae*

Effective treatment for gonococcal infection is a crucial component of efforts to control disease transmission, and is the only way to eliminate disease. Unfortunately, treatment options have dwindled over time as resistance to each new class of antibiotics introduced has developed (29). AMR in *N. gonorrhoeae* develops either through plasmid-mediated mechanisms, chromosomal mutations, or both. Plasmid-mediated mechanisms confer resistance to penicillin and/or tetracycline, while accumulated chromosomal mutations may lead to either single-drug or multi-drug resistance (30). Over time, most AMR *N. gonorrhoeae* originated in the World Health Organization's (WHO) Western Pacific Region and eventually spread around the globe (31).

According to World Health Organization recommendations, an antibiotic must have a cure rate of 95% to be recommended (32). In other words, when the treatment failure rate is 5% or higher for a given antibiotic, it is no longer recommended for use. In spite of continuous monitoring and frequently updated treatment guidelines, *N. gonorrhoeae* has rapidly developed resistance to every class of drugs used for treatment since sulphanomides were introduced in 1936 (33) (Figure 1.2). By the mid-1940s, resistance to sulphanomides was already common (34). Penicillin was introduced at around this time, and was initially shown to be highly effective against gonorrhea (35); within 10-15 years, however, effectiveness was decreasing (36), and by 1989 was no longer recommended for treatment (33). At around the same time, resistance to tetracycline also removed it as a treatment option (37), where it had been used prior for patients in whom penicillin was contraindicated (33). Resistance to fluoroquinolones such as ciprofloxacin, also once highly effective against gonorrhea, was beginning to be reported in the 1990s (38–41); by 2007, they were removed as a treatment option (42). Azithromycin resistance also became widespread at around the same time (33). At this point, third-generation cephalosporins were left as the only monotherapeutic treatment options that could be generally recommended, and were still effective at relatively low concentrations (33). In recent years, resistance to the last line of recommended drugs has been observed in several regions (43–45), potentially ushering in an era of untreatable infections (31), and prompting recommendations to use dual therapy (33).

1.4.1 AMR in China

In China, years of over-the-counter antibiotic availability, coupled with poor antibiotic management and prescribing practices, have resulted in widespread AMR (46). Data from 1,398 isolates collected from STD clinics in 15 cities in China confirm that rates AMR in *N. gonorrhoeae* are high. Almost half (48.5%) exhibited plasmid-mediated tetracycline resistance (TRNG), 37.4% were penicillinase-producing (PPNG), and nearly all (96.6%) showed chromosomal resistance to ciprofloxacin (QRNG); levels of resistance to ceftriaxone and spectinomycin were very low (≤1%) among these isolates (20). Another study indicates that reduced susceptibility to ceftriaxone, however, is highly prevalent (26). Data from the

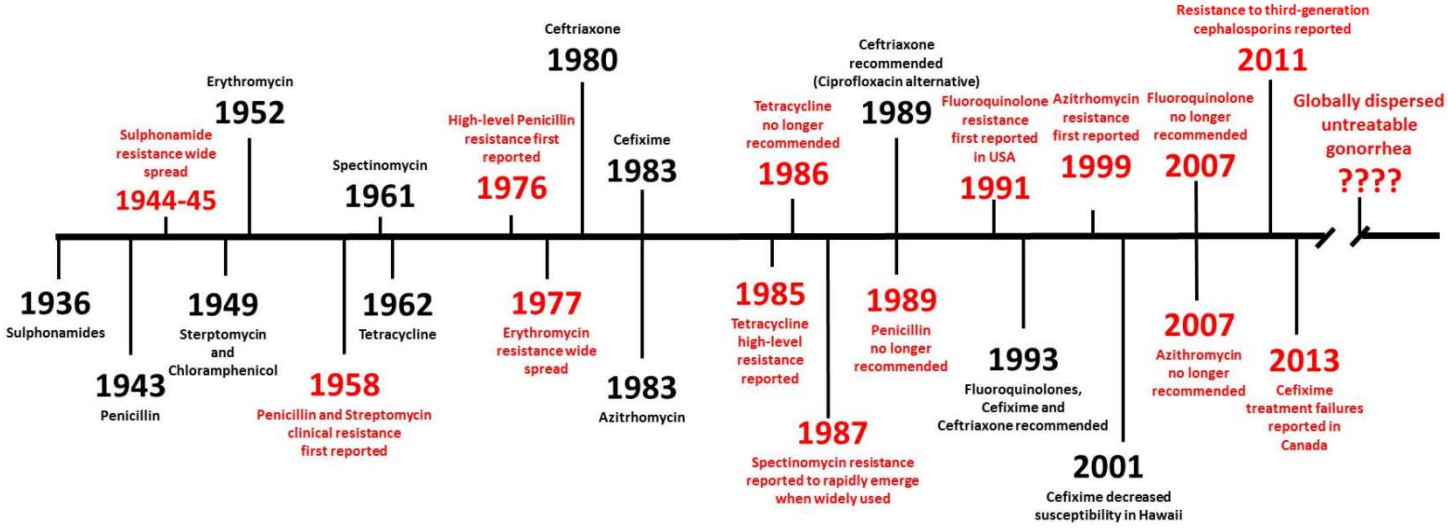


Figure 1.2 History of AMR in *N. gonorrhoeae* (modified from Unemo and Shafer, 2011).

Gonorrhoeae Antimicrobial Surveillance Program (GASP) in the WHO's Western Pacific region showed that decreased susceptibility to oral cephalosporins has been noted in Hong Kong, and that 30-40% of strains in China have decreased susceptibility to ceftriaxone (47).

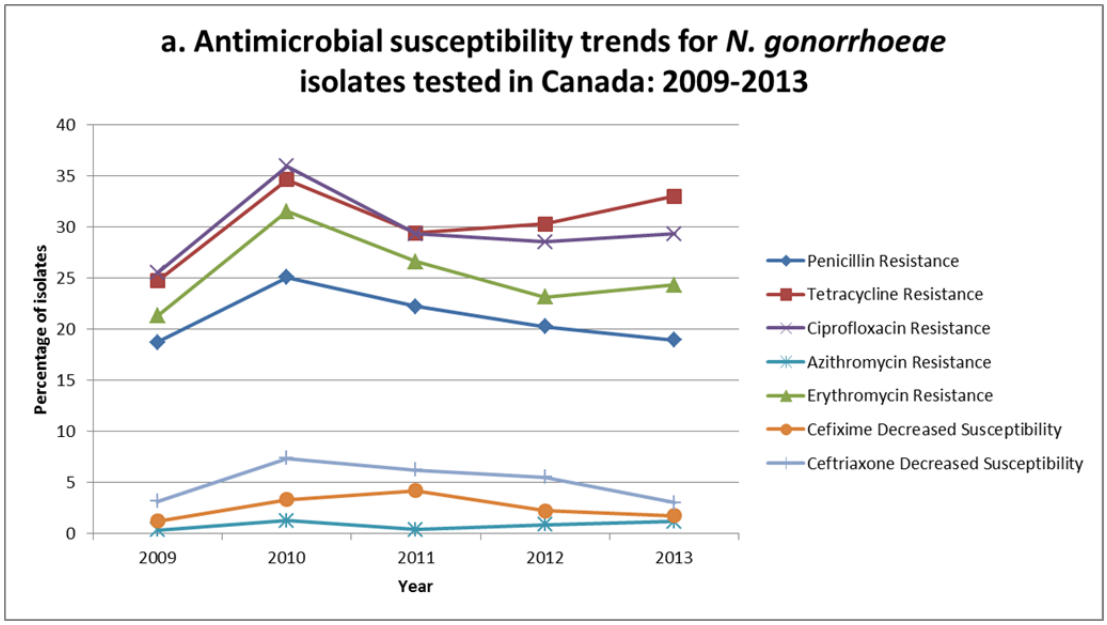
1.4.2 AMR in Canada and Saskatchewan

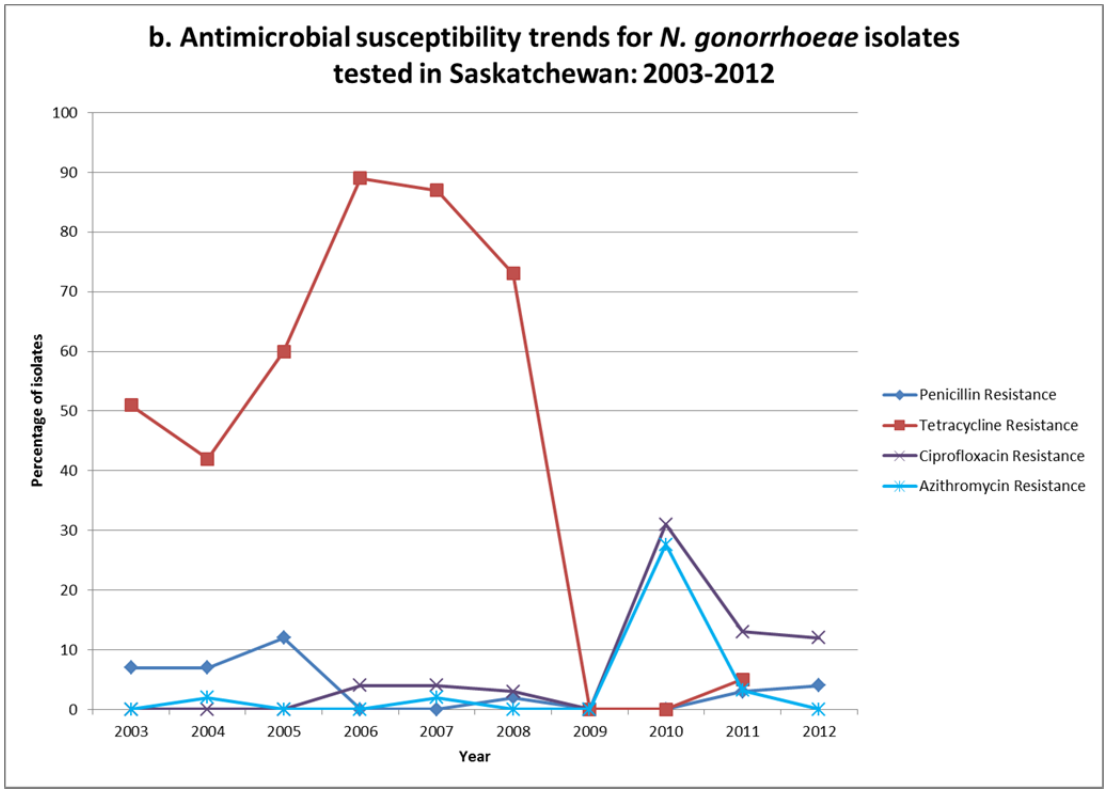
In Canada, AMR is monitored using the passive National *N. gonorrhoeae* Surveillance Program, which relies upon voluntary submission of *N. gonorrhoeae* isolates to the National Microbiology Lab (NML) by provincial labs. Isolates are submitted if the provincial lab identifies resistance to at least one antibiotic, or where AMR testing is not carried out at the provincial level (48).

Rates of AMR in Canada are relatively low, compared to those in China. However, according to a 2015 report, laboratory surveillance data for *N. gonorrhoeae* isolates submitted to the National Microbiology Lab (NML) indicate that rates of AMR have been on the rise since 2009 (49). In 2013, of the 3,195 isolates cultured, 36.1% were resistant to at least one antibiotic. Specifically, 24.3% were resistant to erythromycin, 18.9% to penicillin, 33% to tetracycline, and 29.3% to ciprofloxacin. The proportion of isolates with decreased susceptibility to ceftriaxone (at 0.125 mg/L) and/or cefixime (at 0.25 mg/L) was 3.9%, a decrease from previous years. Only 1.2% of isolates showed resistance to azithromycin—an increase from 0.4% in 2009. (Figure 1.3a) (49)

In Saskatchewan, antimicrobial susceptibility testing is carried out by the provincial Saskatchewan Disease Control Laboratory (SDCL) on cultured samples. In spite of being recommended by the Saskatchewan Ministry of Health (19), cultures are rarely performed; therefore, only a small number of gonorrhea cases are included in surveillance of AMR in the province. It is unknown what percentage of total cases in the province is represented in AMR surveillance data.

Based on the available data, Saskatchewan's rates of AMR are substantially lower than those of the rest of the country (50) (Figure 1.3b). As shown in Figure 1.3b, rates of resistance to penicillin, ciprofloxacin, and azithromycin were quite low from 2003-2009. A spike in resistance to ciprofloxacin and azithromycin was observed in 2010, but by 2012 only tetracycline (5% in 2011) and ciprofloxacin (12% in 2012) resistance remained above the recommended 5% threshold (32).





Sources: PHAC (Canada) and Dev, 2013 (Saskatchewan)

Figure 1.3 Levels of AMR in Canada and Saskatchewan, for selected antibiotics (2003-2012)

1.5 Gonorrhea transmission

1.5.1 Basic reproductive rate

The spread of infection is often characterized by describing the basic reproductive rate, R_0, which indicates the average number of new infections generated by the initial case in a completely susceptible population. The effective reproductive rate, R*, is the average number of new infections generated by the initial case in the current epidemiologic context and therefore also considers the proportion of the population that is susceptible to disease. For an infection to be sustained in a population over time, R* must equal at least 1 (e.g., on average each case successfully transmits the infection to one new susceptible individual). For STIs, R* for any given infection relies upon the probability of infection transmission per contact (β), the contact rate (c) in the population, the duration of infection (d), and the proportion of susceptible people (S). This relationship is expressed by equation 1.1:

$$R^* = R_0 * S = \beta c d * S \quad (1.1)$$

Control of STIs therefore relies upon reduction in one of these parameters. For example, it may be possible to reduce the probability of infection transmission per episode of sexual contact by an increase in the use of condoms. Alternatively, behavioral interventions could result in a decrease in the rate of partner changes (e.g., reduction in c).

1.5.2 Core groups

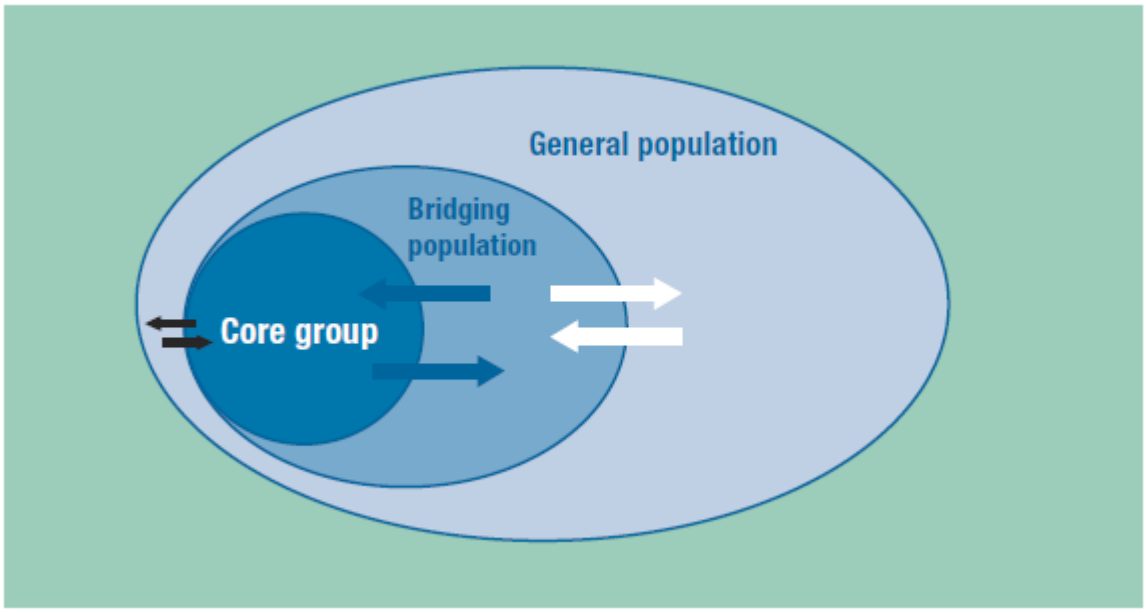
For gonorrhea to persist in a population, R_0 must remain at 1 or above, if we assume the proportion of susceptible individuals in the population at risk approaches 1 and R* approximates R_0. This is a reasonable assumption for gonorrhea because there is no sustained resistance to infection in individuals that have recovered from infection, and no effective vaccine. Brunham (51) notes that there is a critical threshold for the rate of partner change in population required to maintain an STI in a population. By rearranging the equation for the basic reproductive rate, he derives this critical threshold (C_t) as equation 1.2:

$$C_t = 1/\beta d \quad (1.2)$$

and suggests that C_t for gonorrhea is roughly 4 (51). This partner change rate is found in only a small segment of the overall population, known as the "core group," which is defined both by the

behavior of its members and the connectivity between them (51). There are many definitions for the core group (52), and the term has come to be synonymous with "high risk." It may be used to describe those in the sex trade, or those who are street-involved, or exhibit other high risk behaviors. Generally, however, core groups are made up of individuals who have multiple concurrent partners, high rates of partner change, and high rates of infection (51–55). Because of the role of the core group in driving infection transmission, identification of such groups is a fundamental component of effective disease control in any population (32).

In addition to the core group, bridging populations—those low risk individuals who form links between the high risk core, and the general population—are also important for disease transmission (31). Figure 1.4 shows a schematic diagram of the positions and roles of the core group, bridging population, and general population, as it relates to STIs.



Source: WHO 2007

Figure 1.4 Transmission of STIs in the population

1.5.3 Sexual networks

Gonorrhea is a network disease, meaning it requires direct sexual connections between individuals for transmission. Sexual networks are comprised of groups of individuals who are connected to one another—either directly, or indirectly—by sexual contact. Individual members

in a network are known as nodes, or actors, while the connections between them are called ties or edges (56). Study of the structure of networks as they pertain to the flow of disease (or information) is known as social network analysis (SNA); in the case of STIs, the "social network" of primary concern is necessarily a sexual network.

Jolly and Wylie describe three network types related to the transmission of STIs (57):

1. *Sexual networks* are those in which the members have sex with one another, but members may or may not have an STI;
2. *Transmission and infection networks* are those in which at least some members are infected and transmitting infection; and
3. *Disease networks* are those in which members have symptomatic, diagnosed infections.

Wasserheit and Aral (58) offer another way of describing networks, related to epidemic versus endemic disease. Spread networks are those in which $R^* > 1$, and disease is actively spreading. They postulate that these networks comprise subpopulations with high rates of concurrency and high numbers of partners. Maintenance networks, in contrast, are described as those in which $R^* = 1$, and members of these networks have lower rates of partner change, fewer partners, and lower rates of concurrency.

1.6 Epidemiologic tools for gonorrhea control

A variety of epidemiologic tools are available to support research into gonorrhea transmission dynamics and evaluate the effectiveness of interventions for control. Statistical analysis has been the cornerstone of epidemiology for hundreds of years (59), and most epidemiologic studies rely upon biostatistical analytic methods. For example, simple descriptive statistics are useful in providing a deeper understanding of a dataset, and for hypothesis generation, while analytical methods aim to identify associations between causes and outcomes (60). More recently, powerful computer-based techniques have become available to enhance the strength of epidemiologic approaches to understanding disease transmission and control. SNA and dynamic simulation modeling are two newer approaches that are becoming more commonly used in epidemiologic studies.

1.6.1 Social network analysis

SNA refers to the study of social structure (61), and has been used in the social sciences for decades (62). In recent years, interest in network theory methods has been expanding into various other fields, including physics, epidemiology, and biology (63). Social networks consist of a set of individuals or groups who are connected by links that represent their relationships to one another (56). In the case of the spread of STIs, the relationships are sexual, and the links represent sexual contact between individuals. Traditional contract tracing approaches reflect network concepts, in that they attempt to uncover the extent of individuals in the STI transmission chain related to each identified case. The resultant "collection" of individuals represents the sexual network at risk of contracting (or transmitting) infection (64).

Research indicates that network structure has a strong influence on disease transmission, and several studies hypothesize how network structure can be used to inform appropriate interventions (65–69). Uncovering the complete sexual network of interest can be difficult, however, depending on the extent of disease spread and the data collection method employed. There are two basic approaches to establishing sexual networks (70). Egocentric networks are built based upon an initial contact's description of his or her partners; the partners themselves are not followed up, thereby eliminating the possibility of discovering subsequent branches of the network. In contrast, sociometric network approaches aim to elucidate a more complete network by tracing the named contacts and then asking them to name their contacts, in turn. While both study designs have limitations, and uncovering the entire extent of the network is unlikely for large networks, SNA still offers a powerful tool to enhance traditional approaches to the control of gonorrhea, and has been applied in various settings (55,67,70–79). Further, network analysis approaches can be substantially strengthened by combining molecular biological strain information and epidemiologic data (72,75,76,80).

1.6.2 Dynamic simulation modeling

Dynamic simulation modeling offers another powerful approach for the analysis of health data. In the late 1970s, Hethcote, Yorke, and Nold developed a mathematical framework by which to describe the transmission dynamics of *N. gonorrhoeae* (53,54). Since that time, this framework has continued to form the foundation from which other gonorrhea transmission models have been built (81), although modeling techniques have grown more sophisticated over time.

Presently, several different software packages exist to support various different modeling approaches.

There are two main categories of dynamic simulation models of relevance here: system dynamics models and agent-based models (82). System dynamics models—including closely related and mathematically identical compartmental models—are highly quantitative, and use stocks and flows to model the complexities of a given system. These models are based in the concept of feedback and the ways in which it affects the system (83). Such models have been applied to public health questions for almost 50 years (84). Agent-based models are newer, and differ in several ways. Instead of using stocks and flows, agent-based models allow for the modeling of discrete individuals (agents) and their interactions with their environment and one another (85). These models allow for stochastic effects, representation of network and spatial context, longitudinal trajectories of individuals, and the emergence of phenomena based on agent behavior (82); this makes them particularly are well-suited for modeling and evaluating targeted interventions that rely upon an individual's behavior, or position in the network. Agent-based models typically require more time, cost, and skill to build than do system dynamic models, but also offer more flexibility, and enable the modeler to include the effects of stochastics, which is more representative of the real world. The choice of modeling approach, therefore, requires considering the research question and anticipated outcomes in light of these trade-offs.

Models enable researchers to generate and test hypotheses, compare the potential impact of interventions, and predict disease trends under various scenarios, all without requiring access to an actual study population. In this way, models offer an approach that is both time-saving and cost-saving. Depending on the availability of empirical data to inform structure and parameters, and the ultimate goals of the study, models may be more useful for hypothesis generation than providing direct evidence to inform policy decisions. Both are valuable, however, and have great potential to contribute to our understanding of disease transmission and control. Over the last 15 years, a small number of studies have used dynamic simulation models to investigate a questions related to gonorrhea, including AMR development (86,87) and cost-effectiveness of screening or treatment approaches (88–92). Dynamic simulation models offer a unique and valuable opportunity to generate and test hypotheses related to identifying the best possible strategies for the control of gonorrhea—information that is urgently needed.

1.7 Goals and objectives of research

Gonorrhea remains a significant public health concern. Traditional approaches to prevention and control can be strengthened through enhanced understanding of the dynamics of transmission, the potential effect of interventions among different groups, and the factors influencing the development of AMR. Gonorrhea persistence relies on a combination of factors, including both behavioral and biological elements. Successful control methods need to address sociodemographic risk factors for infection and consider rising rates of AMR to be successful. There are a wide variety of epidemiologic tools available for the analysis of these and other issues related to gonorrhea. The body of research presented in this thesis explores the applicability of several epidemiologic methods to improving control of gonorrhea in China and Saskatchewan. Several of the chapters in this dissertation have been published as manuscripts in peer-reviewed journals, and are included in their published form. Approaches presented herein include—alone and in combination—traditional statistical modeling, multi-level statistical modeling, social network analysis, and dynamic simulation modeling, as applied to questions relating to several aspects of gonorrhea control, in different disease settings. The techniques were applied to research questions ranging from the ability to identify sociodemographic risk factors for AMR development in China, to predictors of repeat infection and coinfection in Saskatchewan, to the potential development of AMR *N. gonorrhoeae* in Saskatchewan, in an effort to contribute to existing knowledge about these integral components of disease control. It was hypothesized that the relative power of each approach would be dependent upon the local epidemiology of disease, as well as the availability and robustness of data.

Specific goals of this research included:

1.7.1 Assess the potential of using sociodemographic characteristics to predict the likelihood of infection with AMR N. gonorrhoeae, where rates of resistant infection are high

With rates of AMR increasing globally, and the emergence of resistance to last-line recommended drugs, enhanced understanding of factors contributing to the development of resistance is essential. The research presented in Chapter 2 uses multilevel modeling and focuses on identification of behavioral and demographic risk factors for AMR among a sample of STI clinic clients in Shanghai, China. To date, there are only a small number of published studies on this topic, as reviewed in a paper that I co-authored (93). The studies that do exist are based in a

variety of settings, include different antibiotics, and include a mix of different risk factors, making it difficult to draw any general conclusions (93). The manuscript presented here demonstrates that advanced statistical techniques, such as multilevel multinomial modeling, can be used to elucidate associations between behavioral and demographic characteristics and resistance to antibiotics—even in a population where rates of AMR are extremely high. Additionally, this research illustrates the utility of rigorous statistical techniques for the investigation of complex questions related to sociodemographic variables and mechanisms of AMR.

1.7.2 Identify predictors of bringing a partner to testing and treatment, and safe sex behaviors, where rates of resistant infection are high

Safe sex behaviors and partner follow-up are primary components of STI control. The third chapter of this dissertation focuses on using generalized estimating equations (GEE) to identify predictors of bringing a partner to testing/treatment and use of condoms among a sample of STI clinic clients in Shanghai, China. Identification of such associations can be used to tailor approaches to partner notification as well as target safe sex education to those groups at highest risk, which is particularly important in urban China, where rates of both infection and AMR are high. This chapter contributes new information about the potential value of patient referral partner notification in China.

1.7.3 Identify predictors of repeat gonorrhea and coinfection with gonorrhea/chlamydia in a setting with high infection rates, and low AMR

Chapter 4 presents a study undertaken in a Saskatchewan health region, which aimed to identify risk factors for repeat gonorrhea, as well as for being coinfected with chlamydia at the time of gonorrhea diagnosis. It is one of only two published epidemiologic studies of gonorrhea in Saskatchewan. Using statistical methods including multivariable logistic regression, and mixed-effects multivariable logistic regression, associations between demographic and behavioral characteristics and repeat or coinfection were identified. This research demonstrates the utility of such analysis to inform disease control efforts. The findings presented in this manuscript can be used to inform approaches to counseling and treatment during a clinical visit.

1.7.4 Evaluate the potential contribution of social network analysis to enhancing understanding of gonorrhea transmission dynamics in a setting with high infection rates and low AMR

Chapter 5 focuses on leveraging data derived through SNA to strengthen and clarify previously identified associations between demographic and behavioral characteristics, and the risk of repeat or coinfection (Chapter 4). In addition to providing a visual depiction of the structure of the STI network in the Regina Qu'Appelle Health Region for the first time, this research illustrates the additional contribution of SNA to traditional statistical epidemiologic methods. Further, it highlights the considerable limitations to robust analysis imposed by the current method of STI data collection and storage in Saskatchewan, in contrast to protocols in place in other provinces. This manuscript is the first study to apply SNA to STI transmission in Canada outside of the provinces of Alberta or Manitoba.

1.7.5 Use dynamic simulation modeling to explore scenarios related to the development of AMR in a setting with high infection rates and low AMR

Chapter 6 presents the results of a study to evaluate the contribution of system dynamics modeling to predicting future development of AMR in *N. gonorrhoeae* in Saskatchewan, where infection rates are high, but rates of AMR are low. Based on national trends, it is likely that cephalosporin-resistant *N. gonorrhoeae* will become more and more common in Saskatchewan. Therefore, proactively exploring the potential effects on disease prevalence is prudent. Grounded in empirical data from Saskatchewan, this manuscript builds from the only two published studies that apply system dynamics modeling techniques to questions related to AMR *N. gonorrhoeae*. The results present provocative questions about the potential effects of current treatment and follow-up policies in the context of AMR, as well as further indicate that current systems of STI data collection and storage substantially hinder the utility of such data for epidemiologic analysis.

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CHAPTER 2: BEHAVIORAL AND SOCIOECONOMIC RISK FACTORS ASSOCIATED WITH PROBABLE RESISTANCE TO CEFTRIAXONE AND RESISTANCE TO PENICILLIN AND TETRACYCLINE IN *NEISSERIA GONORRHOEAE* IN SHANGHAI

(Reproduced, with minor edits for the purpose of inclusion, under license; originally published as: Trecker MA, Waldner C, Jolly A, Liao M, Gu W, Dillon JR. Behavioral and socioeconomic risk factors associated with probable resistance to ceftriaxone and resistance to penicillin and tetracycline in *Neisseria gonorrhoeae* in Shanghai. PLoS ONE. 2014;9(2): e89458. doi:10.1371/journal.pone.0089458. My contribution to this work included conception of the analysis, data compilation, data analysis, and writing the manuscript.)

This chapter demonstrates the potential of identifying sociodemographic characteristics of gonorrhea patients associated with antimicrobial resistant (AMR) infection. It establishes the value and power of rigorous statistical modeling as a key component of better understanding gonorrhea transmission and control. The analysis presented in this chapter illustrates the utility of such an approach, even in a setting where both disease rates, and rates of AMR, are high. The results presented in this chapter lay the groundwork for future studies to identify client attributes that may be associated with AMR infection; this could have a substantial impact on the control of disease in both regions like China, where AMR is prevalent, and those like Saskatchewan, where AMR is currently low.

2.1 Abstract

Globally, incidence of *Neisseria gonorrhoeae* infection is once again the highest of the bacterial sexually transmitted infections. The bacterium can produce serious complications in those infected, and emerging resistance to third generation cephalosporins could usher in an era of potentially untreatable gonorrhea. This research aimed to identify risk factors for antibiotic resistant gonorrhea among clients at a Shanghai sexually transmitted infection clinic over two time periods, 2004-2005 and 2008-2011. Demographic and risk factor behavior data, and biological samples for antimicrobial resistance analysis, were collected. Statistical models were built to identify risk factors associated with probable resistance to ceftriaxone and resistance to penicillin and tetracycline. High levels of ciprofloxacin resistance (98%) in our sample precluded examining its risk factors; all isolates were susceptible to spectinomycin. Overall ($P<0.001$), chromosomal ($P<0.001$), and plasmid-mediated ($P=0.01$) penicillin resistance decreased from the first to second period of the study. For tetracycline, chromosomal resistance decreased ($P=0.01$) and plasmid-mediated resistance increased ($P<0.001$) between the first and second periods of study. In multi-level multivariable regression models, male gender ($P=0.03$) and older age ($P=0.01$) were associated with increased minimum inhibitory concentrations to ceftriaxone. Male gender ($P=0.03$) and alcohol use ($P=0.02$) were associated with increased odds of overall tetracycline resistance. Male gender was associated with increased odds of chromosomally-mediated tetracycline resistance ($P=0.04$), and alcohol use was associated with increased odds of plasmid-mediated tetracycline resistance ($P=0.02$). Additionally, individuals in middle-salary categories were found to have lower odds of plasmid-mediated resistance to tetracycline compared with those in the lowest salary category ($P\leq0.02$). This study is one of the first to use multilevel analysis to consider the association between risk factors for gonorrhea and mechanisms of resistance to individual antibiotics. Such information is urgently needed to combat the growing threat of untreatable gonorrhea.

2.2 Introduction

Infections caused by *N. gonorrhoeae* have afflicted human beings for centuries. The organism causes localized infections of the throat, rectum, or urogenital tract and has the potential for serious complications including pelvic inflammatory disease and ectopic pregnancy in women as well as infertility in both sexes (1). Transmission to newborns can lead to serious complications including blindness. Infection with *N. gonorrhoeae* also facilitates HIV transmission (2).

Gonorrhea has become, once again, the most commonly transmitted bacterial sexually transmitted infection (STI) globally (3); it is estimated that 106.1 million cases occur annually around the world (3). Because gonorrhea is often asymptomatic, the true burden of disease is likely much higher.

While gonorrhea has generally been effectively treatable with a single antibiotic dose, drug resistance has emerged to each class of therapeutic agent introduced since the 1940s. Recently, treatment failures to the last-line recommended drugs — third generation cephalosporins — have been reported globally (4–7). The threat of untreatable gonorrhea (8) poses a significant public health challenge both through its associated effects on fertility, birth outcomes, and HIV transmission rates, as well as the potential for increased transmission and complications of infections. Identification of factors associated with antimicrobial resistance (AMR) could help combat this growing epidemic by informing policies around antimicrobial use and targeting intervention programs to those at heightened risk for AMR infection. Behavioral and socioeconomic factors are well known to affect STI transmission (9–12). More research is needed to understand the influence of socioeconomic and behavioral factors on the resistance of *N. gonorrhoeae* isolates to specific antibiotics such as ceftriaxone, including their mechanisms of resistance.

Research into antibiotic resistant *N. gonorrhoeae* infections is particularly relevant in China, where years of over-the-counter antibiotic availability, coupled with poor antibiotic management and prescribing practices, have resulted in widespread antimicrobial resistance (13). We examined the influence of demographic factors as well as previous STIs, use of over the counter antibiotics, and risky sexual practices on the probability of infection with *N. gonorrhoeae* with reduced susceptibility or probable resistance to ceftriaxone, or resistance to penicillin or tetracycline. These analyses are valuable in identifying characteristics that could be used to better target interventions based on risk factor profiles, potentially reducing the need for complex and expensive susceptibility testing in resource limited regions. We combine epidemiologic and previously published biologic data in multi-level analyses for the first time to identify behaviors and client attributes that are associated with an increased risk of infection with AMR *N. gonorrhoeae*.

2.3 Methods

2.3.1 Sample

Epidemiologic and demographic information were obtained from two cross-sectional samples of symptomatic male patients who tested positive for gonorrhea at the Shanghai Sexually Transmitted Infection and Skin Disease Hospital during 2004-2005 and 2008-2011. Partners brought in for evaluation and who consented to participate in the study were also included. Study design and survey descriptions for the first phase of the study (n=483 primary interviews) have been previously published; the second phase (n=299 primary interviews) followed a similar structure (14–18). The analysis presented here included a convenience subsample of 384 cases with complete antimicrobial resistance data.

2.3.2 Epidemiologic data

Staff at the Shanghai Sexually Transmitted Infection and Skin Disease Hospital collected information on demographic variables, including gender, birthdate, salary over the last three months, residency status in Shanghai, district of residence, and level of education attained, as well as STI history, history of antibiotic use, sexual practices, number of partners, and use of alcohol and drugs. Membership in a cluster was abstracted to account for pairs or triples present in the dataset, which arose when any index patient subsequently brought one or more partners to treatment.

2.3.3 Isolate identification and antimicrobial susceptibility determination

The collection, isolation, and identification of *N. gonorrhoeae* isolates has been described previously, as have methods for the determination of minimum inhibitory concentrations (MICs) to ceftriaxone, penicillin, tetracycline, ciprofloxacin, and spectinomycin (18,19). β-lactamase production was determined using nitrocefin and MIC breakpoints were those recommended by the Clinical and Laboratory Standards Institute (CLSI) (19). MIC data were retrieved from data reported earlier (15–17).

2.3.4 Statistical analysis

Two MIC breakpoints were used to explore risk factors for reduced susceptibility (0.03 μg/mL) (20–22) or probable resistance (0.125 μg/mL) (23) to ceftriaxone; separate models were constructed for each breakpoint. The World Health Organization classifies isolates of *N.*

gonorrhoeae with ceftriaxone MICs of ≥0.125 as representing "probable resistance" (23). Two different outcomes were examined for penicillin and tetracycline: overall resistance versus susceptibility, and mechanism of resistance — plasmid-mediated and chromosomally-mediated — versus susceptibility. For penicillin, any isolate with an MIC value < 2.0 μg/mL was classified as susceptible (19) and all other isolates were classified as resistant. Of these resistant isolates, any that were β-lactamase positive were classified as having plasmid-mediated resistance while all others were classified as having chromosomally-mediated resistance (19). For tetracycline, any isolate with an MIC value < 2.0 μg/mL was classified as susceptible, while all others were classified as resistant (19). A breakpoint of 16 μg /mL was used to separate chromosomally-mediated resistance (≥2 and <16 μg/mL) from plasmid-mediated resistance (≥ 16 μg/mL) (19).

Data were managed in Microsoft Excel and Microsoft Access, while all statistical analyses were performed using Stata IC/12.1 (24). Comparisons of demographic characteristics of participants in Phase 1 and Phase 2 were made using Chi-square and Mann-Whitney U tests. To identify predictors of AMR infection, multi-level regression models were built using the gllamm program for generalized linear mixed models (GLMM) in Stata IC/12.1 (24). Six individual models were built to investigate the following outcomes: reduced susceptibility to ceftriaxone at 0.03 μg/ml, probable resistance to ceftriaxone at 0.125 μg/ml, resistance to penicillin, mechanism of penicillin resistance, resistance to tetracycline, and mechanism of tetracycline resistance.

We used logistic regression to investigate the presence or absence of reduced susceptibility or resistance based on MIC data, and multinomial regression models to examine mechanisms of resistance (25). The analysis was limited to relevant independent variables with frequencies > 5% and < 95%, which resulted in a set of 11 variables to be tested (Table 2.1). Phase of study was also initially included as a variable in each model. The continuous predictor variables age and salary were categorized into quintiles for analysis: 14-26 years (n=86), 27-31 years (n=73), 32-37 years (n=69), 38-45 years (n=76), and 46-83 years (n=74) and (in Chinese Yuan) 0-1200 (n=85), 1300-2000 (n=70), 2200-3500 (n=84), 4000-5500 (n=69), and 6000-200000 (n=74).

Intra-class correlation coefficients (ICC) were calculated to determine the amount of variability in the null models for each of the six outcomes accounted for by testing phase of study, membership in a dyad in the dataset, and district of residence as random effects (26). The null

models with the lowest Akaike Information Criterion (AIC) values were selected for building the final models, all of which included district as a random intercept. If < 3% of observations were missing for a particular covariate, listwise deletion was used; otherwise, non-responses were considered as a unique response category.

Only potential risk factors unconditionally associated with the outcome ($p \leq 0.3$) were considered as candidates for inclusion in multivariable models (Table 2.2). Manual backwards elimination was used to build the final model for each outcome. Only significant independent risk factors ($p<0.05$) and potential confounders for each outcome, including age, gender, and study phase, were retained in the final multivariable models. Confounding was recognized when the difference between crude odds ratio for a risk factor-outcome association of interest and the same odds ratio adjusted for the potential confounder was > 10%. After establishing main effects models for each outcome, all possible two-way interactions were considered; only interactions significant at $p<0.05$ were retained in the final models.

Intraclass Correlation Coefficients (ICCs) were estimated as $\sigma^2\text{district} / (\sigma^2\text{district} + \pi^2/3)$ for each final model (27). Plots of standardized residuals were examined for each model to check for outliers.

2.3.5 Ethics statement

Ethical approval for this study was obtained from the Ottawa Hospital Research Ethics Board, the Ethics Committee of the Shanghai Municipal Bureau of Public Health, and the University of Saskatchewan Biomedical Research Ethics Board. Written consent was obtained from all participants. Minors under the age of 18 provided their own consent to participate as they are regarded as emancipated when they take responsibility for seeking reproductive health care. All participants were treated according to Canadian and Chinese STI standard recommendations; no extra procedures were given, other than the time to complete the questionnaire.

2.4 Results

2.4.1 Summary of the study population and AMR findings

Antimicrobial susceptibility data were available for 189 *N. gonorrhoeae* isolates from the first phase of the study and 195 from the second phase for a total of 384 isolates; 337 isolates were from index cases and 47 were from partners brought to treatment. The participants came from 19

different districts of Shanghai; the mean number of cases per district was 11.3 with a range of 1 to 57. Only 16 (4.2%) reported being residents of Shanghai for fewer than 6 months.

There was no significant difference in mean age, education level, previous STI history, use of alcohol or drugs during sex, or reported number of partners in the previous three months between participants from the two study phases. Clients ranged in age from 14 to 83, with a mean age of 35.6 years; 6 clients did not disclose their age. The majority (67.0%) of participants had at least a high school education, and 36 percent of cases reported having had at least one previous STI. Just over one-third (37.3%) of participants reported using alcohol during sex (1 missing), and 7.3% reported using drugs during sex (2 missing). Slightly over half (54.7%) of participants indicated they had 2 or more sexual partners in the last 3 months, and 39.1% said they had only one partner in that time (24 individuals did not respond). (Table 2.1)

For five variables, there were significant differences between phases. Median salary over the previous 3 months reported by Phase 2 participants was higher (3500 Yuan) than that reported by Phase 1 participants (2500 Yuan) ($p \leq 0.001$). In the sample population overall, most cases were male (87.5%); 12.5% of cases were female partners subsequently brought to treatment. However, female partners comprised 17.5% of the Phase 1 population and only 7.7% of the Phase 2 population ($p=0.004$). A higher proportion (31.8%) of participants in Phase 2 as compared to Phase 1 (16.4%) reported having had a previous bacterial STI ($p \leq 0.001$), and 84.6% of Phase 2 participants compared to 64% of Phase 1 participants indicated that they washed their genitals before and/or after intercourse ($p \leq 0.001$); 11 did not respond. Lastly, 19% of Phase 2 participants and 9% of Phase 1 participants indicated previous use of over the counter antibiotic agents ($p \leq 0.001$) (data missing for 74 individuals or 19.3%). (Table 2.1)

Ceftriaxone MICs in our sample ranged from 0.004 to 0.25 μg/mL (Table 2.3). The majority of isolates (75.8%) had reduced susceptibility to ceftriaxone at the 0.03 μg/mL breakpoint, and 10.9% showed probable resistance at the 0.125 μg/mL breakpoint (Table 2.4). Penicillin MICs ranged from 0.125 to 64 μg/mL (Table 2.3). Based on CLSI MIC breakpoints (19), overall, 13.5% of isolates were classified as susceptible to penicillin and 86.5% were resistant over the two time periods tested (Table 2.4). Chromosomally-mediated resistance to penicillin was identified in 36.2% of cases overall, and 50.3% had an isolate with plasmid-mediated penicillin resistance (Table 2.4). Tetracycline MICs ranged from 0.06 to 64 μg/m (Table 2.3). Tetracycline

resistance was present in 54.7% of isolates overall and 45.3% were susceptible based on MIC data (Table 2.4). Chromosomally-mediated resistance to tetracycline was exhibited by 23.7% of isolates overall and plasmid-mediated resistance was found in 31% (Table 2.4).

Because all isolates were susceptible to spectinomycin (MIC range: 2-64 μg/mL) and 98.2% were resistant to ciprofloxacin (MIC range: 0.016-64 μg/mL) (Table 2.3), associations of socio-demographic variables and resistance were not explored for these antibiotics.

2.4.2 Unconditional or crude analysis of predictors for AMR

Level of education, salary, male gender, having reported using drugs during sex, and number of partners reported were unconditionally associated with reduced susceptibility to ceftriaxone at the 0.03 μg/mL breakpoint (Table 2.2); taking over the counter antibiotics, age, male gender, and drug use were unconditionally associated with reduced susceptibility at the 0.125 μg/mL breakpoint. Phase of study, level of education, having reported a previous bacterial STI, practicing genital washing before or after sex, and taking over the counter antibiotics were associated with overall penicillin resistance; the same variables, along with age and salary, were unconditionally associated with the mechanism of penicillin resistance (Table 2.2). Level of education, salary, previous STI, previous bacterial STI, male gender, and reported alcohol use during sex were unconditionally associated with overall tetracycline resistance (Table 2.2). Phase of study, level of education, salary, previous bacterial STI, male gender, and alcohol use were unconditionally associated with the mechanism of tetracycline resistance exhibited (Table 2.2).

2.4.3 Final models of factors associated with reduced susceptibility and probable resistance to ceftriaxone

In the final multivariable models for reduced susceptibility to ceftriaxone (Table 2.5a), men were more likely to be infected with a strain with reduced susceptibility to ceftriaxone with MIC≥0.03 μg/mL (OR=2.2) than women.

Table 2.1 Selected demographic characteristics and risk behaviors of a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital (n= 384)

Variable	Mean (SD), Median (IQR), or N (%)		
	Phase 1 (n=189)	**Phase 2 (n=195)**	**Overall**
Mean age (years) [1]	34.5 (10.0)	36.7 (12.1)	35.6 (11.2)
Median salary (Yuan)*	2500 (1200,4500)	3500 (2000,5500)	3000 (1500,5000)
Gender†			
Male	156 (82.5)	180 (92.3)	336 (87.5)
Female	33 (17.5)	15 (7.7)	48 (12.5)
Education level			
None/less than primary	5 (2.6)	2 (1.0)	7 (1.8)
Primary/middle	61 (32.2)	59 (30.3)	120 (31.3)
High school	63 (33.3)	49 (25.1)	112 (29.2)
Above high school	60 (31.7)	85 (43.6)	145 (37.8)
Previous STI history	69 (36.5)	70 (35.9)	139 (36.2)
Previous bacterial STI*	31 (16.4)	62 (31.8)	93 (24.2)
Wash genitals before or after sex*[2]	121 (64.0)	165 (84.6)	286(74.5)
Take over the counter antibiotics ever*[3]	17 (9.0)	37 (19.0)	54(14.1)
Use alcohol during sex ever[4]	76 (40.2)	67 (34.4)	143(37.3)
Use drugs during sex ever[5]	10 (5.3)	18 (9.2)	28(7.3)
Number of partners in previous 3 months[6]			
One	82 (43.4)	68 (34.9)	150 (39.1)
Two	50 (26.5)	66 (33.8)	116 (30.2)
Three or more	45 (23.8)	49 (25.1)	94 (24.5)

*Significant difference between phases at $p<0.001$

†Significant difference between phases at $p=0.004$

[1]6 missing [2]11 missing [3]74 missing [4]1 missing [5]2 missing [6]24 missing

Table 2.2 P-values for the unconditional associations between participant demographic characteristics, risk behaviors, and resistance to penicillin, tetracycline, and ceftriaxone* from a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital

	Ceftriaxone MIC>0.03	**Ceftriaxone MIC>0.125**	**Penicillin Resistance**	**Penicillin Resistance Mechanism**		**Tetracycline Resistance**	**Tetracycline Resistance Mechanism**	
Variable	*Decreased susceptibility*	*Decreased susceptibility*	*Resistant*	*Chromosomal*	*Plasmid*	*Resistant*	*Chromosomal*	*Plasmid*
Phase of the study (2 : 1)	0.96	0.91	**0.00**	**0.00**	**0.00**	0.37	**0.01**	**0.00**
Education (3 df)	**0.10**	0.47	**0.09**	**0.22**		**0.01**	**0.05**	
Less than primary or no education			Reference category for education					
Primary/middle school	0.51	0.21	0.50	0.23	0.79	0.20	0.29	0.31
High school	0.84	0.12	0.82	0.64	0.56	0.65	0.57	0.85
Above high school	0.72	0.18	0.82	0.65	0.55	0.83	0.68	0.97
Salary (4 df)	**0.23**	0.94	0.61	**0.06**		**0.12**	**0.02**	
<1300 Yuan			Reference category for salary					
1300-2000 Yuan	0.38	0.68	0.84	0.22	0.67	0.86	0.84	0.69
2200-3500 Yuan	0.06	0.98	0.46	0.52	0.45	0.06	0.51	0.01
4000-5500 Yuan	0.83	0.58	0.14	0.05	0.33	0.13	0.53	0.07
6000-200000 Yuan	0.09	0.58	0.51	0.65	0.41	0.95	0.28	0.55
Previous STI	0.87	0.34	0.42	0.38	0.52	**0.12**	0.32	0.42
Previous bacterial STI	0.88	0.75	**0.22**	**0.26**	**0.27**	**0.14**	0.52	**0.09**
Wash genitals before or after sex	0.85	0.40	**0.11**	**0.03**	0.37	0.66	0.70	0.73
Wash genitals (refused)	0.99	1.00	0.33	0.50	**0.22**	0.64	0.34	0.95
Take over the counter antibiotics	0.47	**0.28**	0.67	0.56	0.77	0.64	0.72	0.67
Take over the counter antibiotics (refused)	0.91	**0.14**	**0.01**	**0.02**	**0.01**	0.82	0.52	0.40
Age (4 df)	0.76	**0.04**	0.95	**0.18**		0.83	0.70	
14-26 years			Reference category for age					
27-31 years	0.56	0.77	0.88	0.88	0.78	0.41	0.36	0.62
32-37 years	0.44	0.77	0.91	0.32	0.48	0.99	0.59	0.60
38-45 years	0.71	0.29	0.42	0.52	0.43	0.90	0.41	0.69
46-83 years	0.47	0.02	0.78	0.42	0.92	0.46	0.41	0.67
Male: Female	**0.06**	**0.27**	0.81	0.89	0.83	**0.11**	**0.08**	0.37
Use alcohol during sex	0.58	0.85	0.48	0.62	0.42	**0.01**	**0.03**	**0.05**
Use drugs during sex	**0.22**	**0.24**	0.46	0.57	0.53	0.51	0.68	0.50
Number of partners (3 df)	**0.20**	0.43	0.47	0.33		0.83	0.43	
One partner last 3 months			Reference category for number of partners					
2 partners in last 3 months	0.33	0.42	0.63	0.64	0.72	0.58	0.67	0.21
3+ partners in last 3 months	0.77	0.46	0.40	0.64	0.28	0.47	0.47	0.09
Refused	0.10	0.40	0.33	0.80	0.11	0.81	0.80	0.88

*Reference category for all outcomes was susceptibility as determined by MICs. Variables shown in bold ($p \leq 0.3$) were retained for consideration in building the final multivariable model for each outcome.

Table 2.3 MICs of 384 *N. gonorrhoeae* isolates from Shanghai to ceftriaxone, ciprofloxacin, spectinomycin, penicillin, and tetracycline

	MIC N (cumulative %)														
Antibiotic	*0.004*	*0.008*	*0.016*	*0.03*	*0.06*	*0.125*	*0.25*	*0.5*	*1*	*2*	*4*	*8*	*16*	*32*	*64*
Ceftriaxone	3 (0.8)	24 (7.0)	66 (24.2)	133 (58.9)	116 (89.1)	40 (99.5)	2 (100)	--	--	--	--	--	--	--	--
Ciprofloxacin[1]	--	--	1 (0.3)	--	1 (0.5)	--	--	4 (1.6)	10 (4.2)	40 (14.6)	69 (32.6)	121 (64.2)	103 (91.1)	32 (99.5)	2 (100)
Spectinomycin	--	--	--	--	--	--	--	--	--	2 (0.5)	17 (4.9)	44 (16.7)	159 (47.8)	150 (96.9)	12 (100)
Penicillin	--	--	--	--	--	1 (0.3)	7 (2.1)	12 (5.2)	32 (13.5)	67 (31.0)	48 (43.5)	22 (49.2)	9 (51.6)	18 (56.3)	168 (100)
Tetracycline	--	--	--	--	4 (1.0)	20 (6.3)	31 (14.3)	35 (23.4)	84 (45.3)	59 (60.7)	23 (66.7)	9 (69.0)	26 (75.8)	40 (86.2)	53 (100)

[1]N=383 for ciprofloxacin

Distribution of MICs for 384 *N. gonorrhoeae* isolates to ceftriaxone, ciprofloxacin, spectinomycin, penicillin, and tetracycline. Number of isolates and cumulative percent for each MIC breakpoint are shown for each antibiotic.

Table 2.4 Prevalence of resistance or reduced susceptibility to ceftriaxone, penicillin, and tetracycline in a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital

	Phase 1 N (%)	Phase 2 N (%)	Overall[$] N (%)
Total isolates available	189	195	384
Ceftriaxone			
Reduced susceptibility at MIC≥0.03 μg/ml	143 (75.7)	148 (75.9)	291 (75.8)
Probable resistance at MIC≥0.125 μg/ml[†]	21 (11.1)	21 (10.8)	42 (10.9)
Penicillin			
*Susceptible(MIC<2 μg/ml)**	14 (7.4)	38 (19.5)	52 (13.5)
Resistance overall	175 (92.5)	157 (80.5)	332 (86.5)
Chromosomal resistance	78 (41.3)	61 (31.3)	139 (36.2)
Plasmid-mediated resistance	97 (51.3)	96 (49.2)	193 (50.3)
Tetracycline			
*Susceptible(MIC<2 μg/ml)**	90 (47.6)	84 (43.1)	174 (45.3)
Resistance overall	99 (52.4)	111 (56.9)	210 (54.7)
Chromosomal resistance	62 (32.8)	29 (14.9)	91 (23.7)
Plasmid-mediated resistance	37 (19.6)	82 (42.1)	119 (31.0)

[†]WHO 2012 *CLSI 2009; [$]Phases 1 and 2 combined

The range of MIC values for each antibiotic were as follows: ceftriaxone 0.004-0.25, penicillin 0.125-64, tetracycline 0.06-64.

Table 2.5 (a,b) Results of multivariable analysis for reduced susceptibility and probable resistance to ceftriaxone among a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital (odds ratios (OR) and 95% confidence intervals (95%CI))

a.	Ceftriaxone reduced susceptibility (MIC≥0.03 µg/mL) (n=378)		
Variable	**OR**	**p-value**	**95% CI**
Male : Female	**2.18**	**0.03**	**1.10-4.32**
Age (4 df)		0.58	
14-26 years		Reference category	
27-31 years	0.72	0.40	0.34-1.53
32-37 years	0.63	0.23	0.29-1.34
38-45 years	0.98	0.95	0.45-2.14
46-83 years	0.62	0.21	0.29-1.32
ICC Residential district:	*3.6×10^{-15}*		

b.	Ceftriaxone probable resistance (MIC≥0.125 µg/mL) (n=378)		
Variable	**OR**	**p-value**	**95% CI**
Male : Female	1.64	0.45	0.46-5.84
Age (4 df)		**0.02**	
14-26 years		Reference category	
27-31 years	1.18	0.80	0.35-3.83
32-37 years	0.79	0.73	0.21-2.99
38-45 years	1.51	0.47	0.50-4.57
46-83 years	**3.83**	**0.01**	**1.33-11.01**
Take OTC antibiotics (2 df)		**0.03**	
Do not take OTC antibiotics		Reference category	
Take OTC antibiotics	1.64	0.24	0.71-3.82
Take OTC antibiotics (refused to answer)	**0.25**	**0.03**	**0.07-0.88**
ICC Residential district:	*2.0×10^{-23}*		

Final models for reduced susceptibility to ceftriaxone with significant predictors shown in bold

ICC = Intraclass Correlation Coefficient

Participants who were over 46 years of age were almost 4 times more likely than those from age 14-26 to have probable resistance to ceftriaxone (MIC≥0.125 μg/mL) (Table 2.5b). In addition, those who did not answer the question regarding over the counter antibiotic use were less likely (OR=0.25) to have probable resistance compared to those who did not report over the counter antibiotic use (Table 2.5b). Based on the extremely small ICC values, the effect of district on reduced susceptibility or probable resistance to ceftriaxone was not important after accounting for other risk factors.

2.4.4 Final models of factors associated with penicillin resistance

In the final multivariable models for penicillin resistance (Table 2.6), phase of the study was the only significant predictor. Clients who were in Phase 2 of the study were less likely than those in Phase 1 to be infected with any penicillin resistant strain (OR=0.31), a strain with chromosomal resistance to penicillin (OR=0.26), or a strain with plasmid-mediated resistance to penicillin (OR=0.36). District of residence accounted for 7-8% of the unexplained variance in the penicillin outcomes in the final model (Table 2.6).

2.4.5 Final models of factors associated with tetracycline resistance

While phase was not a significant predictor of tetracycline resistance versus susceptibility (Table 2.7a), the occurrence of plasmid- and chromosomally-mediated resistance to tetracycline did vary based on the phase of the study in the final multivariable model (Table 2.7b). During Phase 2 of the study, individuals were less likely to carry chromosomally-mediated resistant strains than in Phase 1 (OR=0.48), but were more likely to carry plasmid-mediated resistant strains (OR=2.9). The odds of carrying plasmid-mediated resistant strains compared to chromosomally-mediated resistant strains were 5.5 times greater [95%CI 2.96-10.28, $p<0.01$ (data not shown)] in Phase 2 than in Phase 1.

Male gender was a significant predictor of overall tetracycline resistance and chromosomal resistance to tetracycline, but not plasmid-mediated tetracycline resistance. The odds of finding overall tetracycline resistance were 2.1 times higher in men than in women (Table 2.7a); for chromosomal resistance compared to no resistance, the odds were 2.7 times higher in men than women (Table 2.7b).

Table 2.6 Results of multivariable analysis of factors associated with resistance to penicillin based on MIC classification and type of penicillin resistance based on molecular data from a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital (odds ratios (OR) and 95% confidence intervals (95%CI))

	Penicillin Resistance (n=378)			**Penicillin Resistance Type (n=378)**					
				Chromosomal : Susceptible			*Plasmid : Susceptible*		
Variable	**OR**	**p-value**	**95% CI**	**OR**	**p-value**	**95% CI**	**OR**	**p-value**	**95% CI**
Phase 2 of the study :									
Phase 1	**0.31**	**<0.001**	**0.16-0.62**	**0.26**	**<0.001**	**0.12-0.54**	**0.36**	**0.01**	**0.18-0.73**
	ICC Residential district: 0.07			*ICC Residential district for chromosomally-mediated: 0.07*					
				ICC Residential district for plasmid-mediated: 0.08					

Phase of study was the only significant predictor of penicillin outcomes. ICC = Intraclass Correlation Coefficient

Table 2.7 (a,b). Results of multivariable analysis for overall and type of tetracycline resistance from a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital (resistance (odds ratios (OR) and 95% confidence intervals (95%CI))

a.	Tetracycline Resistance (n=376)		
Variable	**OR**	**p-value**	**95% CI**
Male : Female	**2.12**	**0.03**	**1.06-4.25**
Education (4 df)		**<0.001**	
Less than primary or no education	Reference category		
Primary/middle school	2.23	0.35	0.44-10.39
High school	1.02	0.98	0.21-5.01
Above high school	0.76	0.74	0.15-3.78
Alcohol use	**1.69**	**0.02**	**1.08-2.64**
ICC Residential district: 4.4×10^{-10}			

b.	Tetracycline Resistance Type (n=376)					
	Chromosomal : Susceptible			*Plasmid : Susceptible*		
Variable	**OR**	**p-value**	**95%CI**	**OR**	**p-value**	**95% CI**
Phase 2 of the study :						
Phase 1	**0.48**	**0.01**	**0.27-0.84**	**2.85**	**<0.001**	**1.65-4.91**
Male: Female	**2.73**	**0.04**	**1.06-7.05**	1.18	0.70	0.52-2.66
Alcohol use	1.68	0.07	0.96-2.93	**1.93**	**0.02**	**1.13-3.32**
Salary (4 df)				**0.01**		
<1300 Yuan			Reference category			
1300-2000 Yuan	0.78	0.57	0.33-1.84	0.99	0.98	0.46-2.16
2200-3500 Yuan	0.78	0.54	0.35-1.72	**0.28**	**<0.001**	**0.12-0.64**
4000-5500 Yuan	0.77	0.55	0.33-1.81	**0.34**	**0.02**	**0.14-0.81**
6000-200000 Yuan	0.57	0.24	0.22-1.47	0.96	0.91	0.42-2.16
ICC Residential district for chromosomally-mediated: 7.6×10^{-22}						
ICC Residential district for plasmid-mediated: 8.9×10^{-22}						

Final models for tetracycline outcomes with significant predictors shown in bold.

ICC = Intraclass Correlation Coefficient

Both overall tetracycline resistance (OR=1.7) and plasmid-mediated resistance to tetracycline (OR=1.9) were more common among those who reported alcohol use during sex (Table 2.7a,b).

Study participants who earned between 2200 and 5500 Yuan—the middle salary categories—were less likely than those in the lowest salary category (<1300 Yuan) (OR=0.3) to carry strains that exhibit plasmid-mediated resistance to tetracycline. The effect of district on tetracycline resistance was not important based on the extremely small ICC values (Table 2.7 a,b).

2.5 Discussion

This study complements and extends previous work aimed at understanding predictors for AMR in clients with gonorrhea (28–35). The focus of this research, however, was to identify risk factors for resistance or reduced susceptibility to three specific antibiotics, and to identify associations between behavioral factors and mechanisms of resistance to penicillin and tetracycline. Further, we employed a rigorous statistical approach in our analysis, allowing us to better understand the association of individual variables to AMR infection in the presence of a complex set of potential risk factors.

Thirty-six percent of participants in this study reported a previous STI, and 55% reported 2 or more sexual partners in the last three months. While these fractions are higher than several previous studies that have considered prior STI infection status and number of sexual partners among Chinese participants (12,36,37), studies in other countries have noted similar percentages (38). Neither of these factors was associated with an increased risk of infection with reduced susceptibility to ceftriaxone or resistance to penicillin or tetracycline in this study. While previous STIs would plausibly predispose individuals to treatment with antibiotics and potential development of resistance, once an individual has cleared the resistant infection and stopped taking the medication, his or her risk should return to baseline. The absence of the anticipated association between multiple sexual partners and AMR in the present study could be related to misclassification due to social acceptability bias and the relatively high non-response rate for this question.

Probable resistance to ceftriaxone was most common among those in the older age groups. Cole et al. (30) found a similar effect for cefixime in Europe, and Ota et al. (35) found a similar effect for quinolone resistant gonococcal infection in Ontario, Canada. It is possible that this age group

is associating with sex partners of a different demographic than those of the younger age groups, or has other risk factors that were not captured in our study. The possibility of increased risk of resistance at older ages could have important implications for prevention policy in Shanghai, especially in this era of rapidly emerging cephalosporin resistance. Further work to better understand this association is needed; however, this finding does highlight the importance of including a broad range of ages of participants in studies addressing risk factors for AMR.

The findings related to over the counter antibiotic use and probable resistance to ceftriaxone are intriguing. While one might expect to find a relationship between use of antibiotics and AMR infections, we were unable to elucidate such a relationship. The only significant predictor was having failed to provide a response to the question, which cannot be clearly interpreted; this finding is likely related to the relatively high nonresponse rate for this question.

Our results show differences in the prevalence of resistance and type of resistance to penicillin, and to type of tetracycline resistance between the two phases of the study. Because the location of the study clinic moved (within Shanghai) between the two phases of data collection, it is possible that this change over time is the result of unmeasured differences in the populations sampled during the two phases. We were able to control for the influence of the variables listed in Table 2.1 through our multivariable analysis, indicating that the remaining significance of study phase is likely related to unmeasured factors. Clarification of the causes and monitoring of such apparent temporal changes in resistance mechanisms using serial cross sectional and cohort studies could better inform policies around treatment protocols in Shanghai and help to separate the effects of temporal changes from those related to potential unmeasured demographic shifts.

In contrast to our findings for penicillin and tetracycline, there was no apparent difference in the susceptibility to ceftriaxone between the two time periods. Nevertheless, the levels of reduced susceptibility (75.8% at 0.03 μg/mL) were high, and indicate that continued surveillance is critical. Additionally, the 10.9% overall prevalence of isolates with ceftriaxone MICs≥0.125 μg/mL, which is classified as probable resistance by the World Health Organization (23), calls for an alert to be raised at the regional level.

While there has been much research into the association of men who have sex with men (MSM) and antibiotic resistance (28,29,34,39), we found an independent association of male gender

(compared to female) with resistance to tetracycline and reduced susceptibility to ceftriaxone among a sample of men who reported female partners. This could indicate that heterosexual males in Shanghai are at higher risk for tetracycline AMR in general, as well as chromosomally-mediated tetracycline resistance specifically, and ceftriaxone reduced susceptibility compared to females. This finding is consistent with that of Ota et al. (35), who found an unconditional association of quinolone resistant *N. gonorrhoeae* infection in males as compared to females among a population from Ontario, Canada. Further research exploring male gender as a risk factor for AMR is needed to understand what might influence the apparent association in this population. Our results could also indicate that some of the men in this study population were, in fact, MSM. This is especially important in China because stigma and discrimination against MSM might prevent men from truthfully answering questions about sexual partnerships or serve as barriers to seeking health services (40), potentially complicating the association between male gender and AMR. Additionally, the proportion of MSM who also have sex with females has been shown to be high (41), highlighting the need to better understand this population and potential risk for AMR *N. gonorrhoeae* infections in the population as a whole.

The association between alcohol use and tetracycline resistance, both overall and plasmid-mediated, could suggest that those with riskier behaviors were more prone in this population to acquiring plasmid-mediated tetracycline-resistant gonococcal infection. Previous studies have shown that alcohol use is positively correlated with risky sexual behaviors such as having multiple sex partners, risky partners, never using condoms, and infection with STIs (42–45). While the relationship between alcohol use and risky sexual practices and STIs is relatively well-established, the association of alcohol use with plasmid-mediated tetracycline resistance is new. This finding must be considered in the absence of observed associations with other more proximate risk behaviors such as use of over the counter antibiotics and high numbers of partners. It is possible that alcohol use served as a marker for other risk behaviors in our study. For example, those using alcohol could be members of a network of individuals who have a higher risk of STIs, are using antibiotics for treatment, and, consequently, are more likely to carry resistant strains. The relationship we found between alcohol and plasmid-mediated tetracycline resistance, specifically, could reflect that the predominant strains being passed through this network at the time of the study had plasmid-mediated tetracycline resistance, given there is no biologically plausible explanation for an association between alcohol use and

mechanisms of resistance. At the least, our findings suggest the need to further explore the relationship of such risk behaviors and exposure to AMR in general as well as to specific types of AMR strains to clarify this relationship. Such information would be especially useful in settings where individuals do not provide complete or truthful answers to questions about more immediate risk factors.

The finding that plasmid-mediated tetracycline resistance was less common in middle salary categories compared to those in the lowest salary category could be related to socio-demographic factors. However, this relationship was not found for the other outcomes under investigation. There is a possibility that individuals with mid-level incomes are associating with partners with different exposure histories than those with lower incomes. Associations of income category to infections with STIs /HIV have been found in other studies (11,12); however, further, targeted research would be needed to explore the association identified in our study.

This study had several limitations. Foremost, the relatively small sample size of participants with characterized *N. gonorrhoeae* isolates, drawn from a population where antimicrobial resistance is extremely prevalent (14), limited the potential to explore outcomes within this dataset to the three antibiotics that exhibited some variability in resistance patterns. The participants were all drawn from the same medical clinic, and had very similar questionnaire responses. As well, the study population consisted of all male index cases, and their recruited female partners, which precludes direct comparison of the characteristics of male and female index cases. Missing data also limited the initial choice of variables to be considered for model building from the more substantial list of the original questions. It is also likely that there was under-reporting of some risk behaviors (46). Further, because the location of the clinic moved between the two phases of data collection, it is difficult to differentiate temporal shifts in AMR prevalence from other unmeasured differences between the two populations. However, we tested all of the variables listed in Table 2.1 as part of the model building process, and included in the final model any variables shown to have a confounding effect. This analytical approach controls for the influence of measured differences in the two populations related to these factors on the other variables in the final models. Also, it is likely that the relatively high rate of nonresponse related to antibiotic use contributed to the failure to see an association between over the counter antibiotic use and reduced susceptibility or resistance.

In conclusion, although there was a high prevalence of resistance in the isolates tested (18), we were able to identify several risk factors for infection with gonococcal infection with reduced susceptibility or probable resistance to ceftriaxone, resistant to penicillin and tetracycline, and also for the mechanism of resistance to penicillin and tetracycline. The use of multi-level regression analysis to account for potential clustering in the data and explore multinomial outcomes strengthens the study and represents a thorough and sophisticated approach to analysis of such data. We have laid the groundwork for further studies to better understand behavioral factors associated with infection with resistant *N. gonorrhoeae* —knowledge that is central to tailoring effective policies for combatting the emergence of untreatable gonorrhea focused on targeting behavioral risk factors.

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CHAPTER 3: FEMALE PARTNER NOTIFICATION IS A PROMISING PREVENTION STRATEGY FOR CONTROLLING STIS IN SHANGHAI: DEMOGRAPHIC AND BEHAVIORAL DATA FROM A SHANGHAI CLINIC

(Reproduced, with minor edits for the purpose of inclusion, with permission; originally published as: Trecker MA, Gu W, Jolly A, Waldner CL, Dillon J R. Female partner notification is a promising prevention strategy for controlling sexually transmitted infections in Shanghai: Demographic and behavioral data from a Shanghai clinic. Sex Transm Dis. 2014;41(12):702-5. My contribution to this work included conception of the analysis, data compilation, data analysis, and writing the manuscript.)

In both China and Saskatchewan, rates of gonorrhea remain high. Partner notification, along with safe sex behaviours, and appropriate, effective treatment, is a key component of disease control. This manuscript demonstrates that partner notification has potential as a strategy for STI control in China, where it is currently not widely-implemented. Additionally, robust statistical analysis is shown to be useful for the identification of characteristics of male gonorrhea patients that were associated with the presentation of an associated female partner, and the use of condoms with the partner. Identification of client attributes that can be used by the clinicians to tailor their approach to contact tracing or counseling may provide an additional, useful approach to disease control in settings where incidence is high.

3.1 Abstract

We identified predictors of partner presentation and condom use among male gonorrhea patients in Shanghai, China. Stable relationships, intercourse in the preceding week, and longer duration of symptoms were associated with partner presentation. Men were more likely to use condoms with their spouse and if they were 35 or under.

3.2 Introduction

While intensive efforts by the Chinese government to eliminate sexually transmitted infections (STIs) initially resulted in low prevalence during the middle of the 20th century, there has been a resurgence in incidence since the 1980s (1). Encouraging partner notification is an important case-finding strategy for controlling STI transmission (2). The objectives of this study were to identify factors associated with partner presentation after STI diagnosis and factors associated with condom use among male STI clinic clients with laboratory confirmed gonorrhea in Shanghai, China, where rates of gonorrhea are particularly high (3).

3.3 Methods

We used a convenience sample of symptomatic male patients who tested culture positive for *Neisseria gonorrhoeae* at the Shanghai Sexually Transmitted Infection and Skin Disease Hospital (SSTISDH) during two periods—2004 to 2005 and 2008 to 2011—who also agreed to provide epidemiologic and demographic information. The SSTISDH is the only facility in Shanghai specializing in STIs, and the only one accredited by the standards of Western Medicine. The SSTISDH diagnoses roughly 700-800 gonorrhea cases per year, representing 14-16% of the city's annual gonorrhea case load. Participating patients were referred to trained interviewers by attending physicians. A consent form and an anonymous questionnaire were administered to each patient to gather demographic information, STI history, and information related to sexual practices. Patients were also asked to identify (by name, alias, or initial) up to 10 partners they had sex with in the last three months, and to describe the relationship using a standard questionnaire. Roughly 30% of culture positive cases consented to an interview; the most common reason for declining was lack of time because of the need to get back to work.

The interviewers asked patients to inform their partners of potential STI exposure and to encourage them to present at the clinic. They were provided with cards with the clinic address and contact information for the study, as well as an ID number linking the card to the index case,

to give to their sex partners to invite them to participate. Each partner was tested and completed a questionnaire similar to that of the index case, with the exception of partner-specific questions.

Data were analyzed using Stata IC/12.1 (4) and SPSS 21.0 (5). Differences between the index males and their presenting partners were examined using Chi-square and Mann-Whitney U tests. The brought-to-treatment index (BTI) (6) was calculated by dividing the number of new cases brought to treatment by the number of index cases interviewed and advised to notify their partner. To account for presentation of more than one partner, generalized estimating equations (GEE) with a logit link function were used to examine risk factors associated with bringing a partner to treatment and for not using condoms. The final multivariable models were built using manual backwards elimination considering only potential risk factors unconditionally associated with the outcome where $p \leq 0.2$. Only significant independent risk factors ($p<0.05$) and potential confounders for each outcome were retained in the final multivariable models.

3.4 Results

The 567 index male clients in our study ranged in age from 14 to 83 years, with a mean age of 35.8 years. Just under half of index cases (40.2%) reported having a previous STI. The median duration of symptoms reported was 3 days. Of those with symptoms, 22.4% reported having had sex while symptomatic. Only 18.2% of index cases reported “ever” using condoms with their partner, and just 7.6% reported using a condom at last sex with their partner. (Table 3.1a)

Of the 567 index male cases included in the study population, 136 men (Table 3.1b) subsequently referred 158 female partners for testing and treatment (Table 3.1c). There were significant differences in the mean age, median income over the last 3 months, residency status in Shanghai, education level, job type, previous STI status, duration of symptoms, current symptomatic status, sexual contact while symptomatic, and alcohol use reported between the men and their partners (Table 3.1b,c).

The 567 index males described 765 heterosexual relationships (Table 3.2). Of these, 158 female partners subsequently presented for testing and treatment, 107 of whom (68%) were culture positive for gonorrhea. A BTI of 0.19 was calculated based on the number of positive female partners identified from the interviews completed with index male clients. Per index case

Table 3.1 Demographic and behavioral characteristics of 567 index males, 136 males with presenting partners, and 158 female partners from a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital

Characteristics [n (%), mean (SD), or median (IQR)]	a) All index males n=567	b) Males with presenting partners n=136	c) Presenting female partners n=158
Mean age*	35.8 (11.0) n=563	34.1 (10.3) n-134	29.6 (9.5) n=156
Median income in last 3 months*	3000 (2000,5000) n=565	3000 (1650,5500)	2000 (600, 3000)
Official resident of Shanghai*	389 (69.0) n=566	95 (69.9)	75 (47.5)
Highest level of education*			
Primary or below	124 (21.9) n=564	9 (6.6)	30 (19.0)
Middle/Highschool	235 (41.5)	69 (50.7)	97 (61.4)
Above Highschool	208 (36.7)	58 (42.7)	31 (19.6)
Type of work†			
Laborers	88 (15.6) n=563	29 (21.3) n=135	15 (9.7)
Service Industry	63 (11.2)	19 (14.0)	13 (8.4)
Professional	337 (59.9)	71 (52.2)	75 (48.4)
Other	8 (1.4)	2 (1.5)	7 (4.5)
No job/retired	67 (11.9)	14 (10.3)	35 (22.6)
CSW	--	--	10 (6.5)
Median age at first sex	21 (19,24) n=539	20 (18,22) n=135	21 (19,23) n=153
Previous STI ever*			
Yes	228 (40.2)	64 (47.4) n=135	11 (7.0)
No	336 (59.3)	71 (52.6)	147 (93.0)
Unsure	3 (0.5)	0 (0)	0 (0)
Median duration of symptoms (days)*	3 (2,5) n=561	3 (2,5) n=135	12 (7,24.5) n=84
Currently symptomatic*	562 (99.1)	136 (100)	81 (51.3)
Sex while symptomatic (% of those symptomatic)*	127 (22.4)	45 (33.1)	44 (54.3)
Alcohol before or during sex last 12 months*	233 (41.1)	53 (39.0)	31 (19.6)
Psychogenic drugs before or during sex last 12 months	55 (9.7)	12 (8.8)	7 (4.4)
"Ever" condom use with this partner	87 (18.2) n=477	25 (19.7) n=127	--
Condom use at last sex with this partner	39 (7.6) n=516	14 (10.3)	--
Given something in exchange for sex	255 (49.5) n=515	44 (32.4)	--
Received something in exchange for sex	45 (8.7) n=515	16 (11.8)	--

Characteristics of all index males, subset index males with presenting partners, and female partners who presented for testing. Significant difference among characteristics between population of males who brought partners and their female partners indicated by: * $p<0.001$, † $p=0.002$

interviewed, 0.19 new cases were identified and treated; in other words, 5.3 index cases needed to be interviewed to find one new case in this study population.

Odds of partner presentation were higher if the partner was classified as a temporary unpaid partner (OR 1.92), a "lover" (OR 4.12), or a spouse (OR 2.67), as compared to temporary paid relationships (Table 3.3). There was no difference in the odds of presentation between temporary unpaid partners and spouses (OR 0.72, 95%CI 0.39 to 1.32, p=0.29) or between presenting a "lover" compared to a spouse (OR 1.55, 95%CI 0.94 to 2.55, p=0.09). Partner presentation was also more likely if the index case reported having had sex with the partner in the last week (OR 2.42) or having experienced symptoms for longer than 3 days (OR 1.89) (Table 3.3).

Increasing age was associated with decreasing odds of reporting "ever" use of condoms with the partner. Compared to clients more than 45 years old, those from age 14-25 (OR 9.51), 26-29 (OR 6.16), and 30-35 (OR 5.71) years were more likely to report "ever" using condoms (Table 3.4). Condom use was more likely (OR 3.45) when the partner was identified as a spouse compared to a temporary paid sex partner (Table 3.4). Clients were also more likely (OR 2.13, 95%CI 1.27-3.56, p=0.004) to use a condom with a spouse than with a lover. "Ever" condom use (OR 1.06) increased with increasing age in years at sexual debut (p=0.05) (Table 3.4), and confounded the relationship of age and "ever" condom use.

Table 3.2 Partners described and brought to testing and treatment by 567 index males with gonorrhea diagnosed at the Shanghai Sexually Transmitted Infection and Skin Disease Hospital

		Number of Partners who Presented					
		0	**1**	**2**	**3**	*Total*	*Total Described*
Number of Partners Described	**0**	48	3	0	0	*51*	*0*
	1	250	69	2	1	*322*	*322*
	2	103	40	4	0	*147*	*294*
	3	23	12	2	3	*40*	*120*
	4	3	2	0	1	*6*	*24*
	5	0	1	0	0	*1*	*5*
	Total	*427*	*127*	*8*	*5*	567	765
	Total Presented	*0*	*127*	*16*	*15*	158	

A total of 567 index males described 765 heterosexual relationships. 158 female partners were subsequently brought for testing. Note that for some cases, female partners presented at the clinic even though the associated index male did not provide descriptive information about any partners.

Table 3.3 Final multivariable model of predictors of partner presentation among a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital.

Variable	OR	p-value	95% CI
Relationship type (4 df)		**<0.001**	
Temporary paid		reference category	
Temporary unpaid	**1.92**	**0.04**	**1.02-3.60**
Lover	**4.12**	**<0.001**	**2.31-7.37**
Spouse	**2.67**	**<0.01**	**1.41-5.02**
Refused/unsure	0.56	0.29	0.20-1.60
Sex this week	**2.42**	**<0.001**	**1.60-3.68**
Symptoms for more than 3 days	**1.89**	**<0.01**	**1.26-2.85**

Variables in bold are significant at $p<0.05$.

Table 3.4 Final multivariable model of predictors of "ever" condom use among a sample of clients from the Shanghai Sexually Transmitted Infection and Skin Disease Hospital.

Variable	OR	p-value	95% CI
Age (4 df)		**<0.001**	
Age 14-25	**9.51**	**<0.001**	**3.90-23.21**
Age 26-29	**6.16**	**<0.001**	**2.55-14.87**
Age 30-35	**5.71**	**<0.001**	**2.49-13.06**
Age 36-44	1.3	0.57	0.52-3.25
Age 45+		reference category	
Relationship type (4 df)		**<0.001**	
Temporary paid		reference category	
Temporary unpaid	0.67	0.36	0.28-1.58
Lover	1.62	0.09	0.93-2.82
Spouse	**3.45**	**<0.001**	**1.98-6.02**
Refused/unsure	1.2	0.68	0.52-2.78
Age at sexual debut	1.06	0.05	1.00-1.13

Variables in bold are significant at $p<0.05$.

3.5 Discussion

Our BTI estimate is comparable to other gonorrhea studies in the region (7), and slightly lower than Brewer's reported median of 0.25 (range: 0.09-0.58) from a review of 21 reports from developed nations between 1975 and 2004 (2). However, it is high given the unaccustomed invasion of privacy, lack of partner notification guidelines, and limited time and training levels of staff (7). In addition, the 68% of evaluated partners who were culture positive for gonococcal infection in our study is higher than the median 37.9% diagnosed with an STI from a recent systematic review of partner notification uptake in China (7), indicating patient referral partner notification could play an important role in reducing STIs in urban China, if it were more widely utilized. In addition to increased efforts focused on populations less likely to refer their partners, provider referral (whereby healthcare providers notify the partners) or conditional referral (whereby cases are given the chance to notify their partners, but follow-up is carried out by healthcare providers) could further increase partner presentation success rates in urban Chinese settings.

Our finding that identifying the partner as a "lover" was associated with greatest odds of partner presentation when compared to a temporary paid partnership, and that men were no more likely

to refer a spouse than a temporary partner for testing, were surprising. In a 2002 study of male STI patients in China (8), only 23% of men who lived with their spouse indicated that they were willing to inform them of their STI status. For a man to inform his spouse that he has an STI could suggest infidelity, which is generally considered to be unacceptable in Chinese society, though not uncommon (9). Focusing counselling efforts—found to improve success of partner notification (10)—on those in relationships where the partner is least likely to be notified could potentially increase effectiveness. Our finding that men who had not had sexual contact in the previous week, and those who had symptoms for fewer than three days, were less likely to bring a partner for testing are concerning. Because men can have asymptomatic infections, or delayed onset of symptoms (11), even men who had not engaged in sexual contact in the last week could have infected their partners unknowingly. Those who had only recently become symptomatic could similarly have infected their partners before symptom onset, making notification of partners even more important.

Our finding that condom use was more likely with a spousal partner was unexpected, since others have found that likelihood of condom use decreases with increasing permanence of relationship (12–14). Our study shows the opposite effect, and we are aware of only one other study in China that shows a similar finding (15). Low condom use with casual/paid partners versus spouses in our study, coupled with overall low use of "ever" condom use among this population, highlights the potential for transmission of STIs and HIV among paid, casual, and spousal partners. Our finding that younger age groups are much more likely to use condoms than older age groups is supported by previous studies in China (16), and is concerning because older individuals in China represent a growing proportion of the country's total STI burden (16).

Because participants were from the same medical clinic, the generalizability of the findings is limited. Specific questions about MSM status were not included in the survey, due to an anticipated low response rate to such questions based on stigma (17), so we were unable to explore the potential influence of men who have both male and female sex partners. Also, we did not elicit further contacts from partners who presented, limiting the extent of the network-at-risk. Additionally, it is possible that bias may have been introduced into the study based on potential differences between responders and non-responders; unfortunately, demographic information about non-responders was not collected. Lastly, it is possible that partners of infected cases may

have been informed and either presented elsewhere, or not self-identified upon presentation, which could result in an underestimate of our BTI.

In spite of the study limitations and current low levels of implementation (18), our results indicate that patient referral partner notification could be an important case-finding strategy in Shanghai. This is also one of few studies reporting higher likelihood of condom use with spouses than with temporary paid partners. These findings are especially important in Shanghai, and potentially other urban Chinese settings, in the context of growing resistance to cephalosporins by *N. gonorrhoeae* (19). In addition to adopting a provider or contract referral approach, control of STIs in this population can potentially be improved by focusing increased partner notification efforts on men who are in temporary relationships, have recently developed symptoms, and who have not had sexual contact in the preceding week. Older STI clients and those in temporary or paid sexual relationships would benefit most from education on condom use.

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CHAPTER 4: DEMOGRAPHIC AND BEHAVIOURAL CHARACTERISTICS PREDICT BACTERIAL STI REINFECTION AND COINFECTION AMONG A CROSS SECTIONAL SAMPLE OF LABORATORY-CONFIRMED GONORRHEA CASES IN A LOCAL HEALTH REGION FROM SASKATCHEWAN, CANADA

(Reproduced, with minor edits for the purpose of inclusion, with permission; originally published as: Trecker MA, Dillon JR, Lloyd K, Hennink M, Waldner CL. Demographic and behavioural characteristics predict bacterial STI reinfection and coinfection among a cross-sectional sample of laboratory-confirmed gonorrhea cases in a local health region from Saskatchewan, Canada. Can J Public Health. 2015;106(2), e17-e21. My contribution to this work included conception of the study, obtaining ethics certification, onsite collection of all included data, data analysis, and writing the manuscript.)

In Saskatchewan, rates of gonorrhea are high, while antimicrobial resistance is relatively rare. Current strategies for disease control have failed to result in lower disease rates, indicating new approaches may be warranted. Similar to the findings from China, this chapter provides further evidence that certain client attributes, which can be elicited during a clinic visit, can help clinicians tailor an appropriate approach to treatment and counseling. In urban Saskatchewan, using such attributes to guide the use of presumptive dual antibiotic therapy and/or expedited partner therapy could have important implications for the control of gonorrhea. Using client characteristics to better tailor an approach could provide improved disease control in contrasting regions, such as China and Saskatchewan.

4.1 Abstract

Objectives: We aimed to identify demographic and behavioural determinants associated with risk of repeat STI infection and coinfection with gonorrhea and chlamydia in the Regina Qu'Appelle Health Region, Saskatchewan.

Methods: We extracted data from a cross-sectional sample of laboratory-confirmed gonorrhea cases between 2003 and 2012 from the notifiable disease files of the Regina Qu'Appelle Health Region. Risk factors for repeater status were examined using logistic regression and for coinfection with gonorrhea and chlamydia using mixed-effects logistic regression to account for multiple diagnoses for individual clients.

Results: Data from 1143 cases (representing 1027 unique individuals), and 1524 reported contacts (representing 1383 unique individuals) were extracted from the 10-year period. Factors associated with repeat infection entries in the database included younger age at first visit ($p=0.01$), coinfection ($p=0.01$), and sex trade involvement ($p<0.01$). Factors associated with coinfection at the time of diagnosis included younger age at diagnosis ($p<0.001$) and reported alcohol or drug abuse ($p=0.04$).

Conclusion: In one of the first epidemiologic studies on gonorrhea in Saskatchewan, we have identified age, engagement in the sex trade, and drug and alcohol abuse as potential markers to identify clients with a high risk of reinfection and coinfection in the Regina Qu'Appelle Health Region. This information can help health care professionals in Saskatchewan's urban centres personalize their approach to counseling and treatment to optimize patient outcomes and disease control efforts, including potentially using expedited partner therapy, and/or dual therapy where indicated.

4.2 Introduction

In spite of the apparent progress to curb gonorrhea during much of the 1990s, reported cases have been slowly increasing in Canada since 1999. According to 2011 data, Saskatchewan's gonorrhea rate of 71.7 per 100,000 is second only to Manitoba among the provinces—more than twice that of Ontario and Quebec, as well as the Canadian national average of 33.1 per 100,000 (1). In addition to possible complications such as pelvic inflammatory disease, infertility, disseminated infection, and the potential for vertical transmission (2), gonococcal infection also

results in an estimated 3-5-fold increase in HIV transmission rates (3). Saskatchewan's extremely high and increasing rates of gonorrhea, coupled with its burgeoning HIV epidemic (4), illustrates the critical need for better understanding and control of gonorrhea transmission in the province, especially in light of the emerging threat of untreatable gonorrhea (5). A first step toward identifying why gonorrhea rates are increasing in Saskatchewan is to characterize the current STI population in the province. However, to date there has been only one published epidemiologic study of STIs in Saskatchewan (6).

The objectives of this research were to describe demographic and behavioural risk factors from gonorrhea cases in the Regina Qu'Appelle Health Region (RQHR), and to identify predictors of repeat infection and coinfection with gonorrhea and chlamydia.

RQHR is located in south-central Saskatchewan and serves 260,000 residents, including those of Saskatchewan's capital city, Regina. It is the second largest health region in Saskatchewan, and has recorded an average of roughly 100 cases of gonorrhea and 1000 cases of chlamydia each year since 2008.

4.3 Methods

4.3.1 Sample

Gonorrhea is a notifiable disease in all Canadian provinces; in Saskatchewan, all cases confirmed by the provincial Saskatchewan Disease Control Laboratory (SDCL) are reported to public health authorities. In accordance with national guidelines, contact tracing is initiated in the event of a positive laboratory diagnosis, and includes individuals who were contacts within 60 days prior to the test date. Contact tracing is generally carried out by public health staff in the event that index cases do not notify their contacts.

We accessed the notifiable STI files from RQHR to extract the records for all laboratory-confirmed gonorrhea cases—including those concurrently infected with chlamydia—from January 1, 2003 to December 31, 2012. Every positive gonorrhea case recorded in RQHR over this time period was included in the dataset. The files contain demographic information including name, health services number (HSN), age, date of birth, and address; event-related information including diagnosing facility, laboratory tests reported, and type and date of treatment; and, risk factor information including sexual history, drug and alcohol use, and number of partners.

Information on sexual contacts and their follow-up was also recorded. Information on all contacts who presented and had a laboratory-confirmed infection also became part of the case file.

4.3.2 Data management and analysis

Microsoft Access (7) was used to create a digital database that preserved the linkage between cases and their named contacts. Because files were in hardcopy format for the first eight years of the dataset, all data abstraction was done on-site at health region offices. This study was approved by the research ethics boards of both the University of Saskatchewan and RQHR (No. 12-323 and 12-98, respectively). Prior to removal from health region offices, personal identifiers, including last name and address, were removed. Additionally, an algorithm was applied to scramble clients' HSNs to anonymize them while preserving the ability to recognize repeat occurrences of disease in individuals during the 10-year study period. Urban versus rural place of residence was abstracted using the first three digits of cases' reported postal codes; a "0" as the middle digit indicates a rural area, while any other number indicates an urban area (8).

After the data were de-identified, descriptive analyses were carried out using Microsoft Excel (9) and Stata IC/12.1 (10). The continuous variable age was categorized prior to analysis. For the purpose of this analysis, we defined "repeater" as someone who appeared two or more times in the 10-year database. For repeat infections occurring at intervals of 2 months or less, we verified that appropriate, observed therapy (dual azithromycin and cefixime) was administered for the prior infection, to rule out persistent infection as opposed to repeat infection. Based on Saskatchewan's extremely low levels of antibiotic resistance (11), treatment failure is unlikely in these cases. Differences in characteristics between males and females were investigated using chi-square tests. Observations for two cases with outlying ages (4 months and 78 years of age) were dropped prior to multivariable analysis.

A multivariable logistic regression model was built to identify factors associated with having repeat entries in the database, using one entry per person, based on characteristics at first entry and controlling for amount of follow-up time.

To identify variables associated with being coinfected with gonorrhea and chlamydia at the time of visit, a mixed-effects multivariable logistic regression model was built using a random

intercept to account for clustering by participant identification (anonymized HSN) due to repeat entries.

Both models were built using manual backwards elimination and only potential risk factors unconditionally associated with the outcome ($p \leq 0.2$) were considered as candidates in building the final multivariable models for each outcome. For multiple-category predictors, inclusion in the model was based on the results of a type 3 Wald test. Only significant independent risk factors ($p<0.05$) and important confounders were retained in the final multivariable model for each outcome. Confounding was recognized when the difference between crude odds ratio for a risk factor-outcome association of interest and the same odds ratio adjusted for the potential confounder was > 10%. After establishing main effects models for each outcome, all possible two-way interactions were considered; only interactions significant at $p<0.05$ were retained in the final models.

The intraclass correlation coefficient (ICC) was estimated as $\sigma^2 \text{patientID} / (\sigma^2 \text{patientID} + \pi^2/3)$ for the final coinfection model (12). Plots of standardized residuals were examined for each model to check for outliers.

4.4 Results

4.4.1 Study population

There were 1143 occurrences of laboratory-confirmed gonococcal infection in the health region from 2003-2012, representing 1027 unique individuals. From these 1143 case visits, 1524 contacts were elicited, representing 1383 unique individuals. Just over half of cases (55.2%) were female. Male cases were older than female cases ($p<0.001$) and were less likely to be coinfected than females ($p<0.01$) (Table 4.1). The mean age difference between partners was 4 years (SD 4.9 years, data not shown). Most cases came from urban areas. Roughly 8% of female cases were pregnant at the time of diagnosis. The most frequently reported risk factors for both sexes were unprotected sex and having had two or more partners in the last 6 months. Least frequently reported risk factors were sex trade involvement (for either the case or their contact) and same sex partnerships. Males were more likely than females to report same sex partners ($p<0.001$) and less likely to have had a previous STI ($p<0.01$). The majority of cases were treated at locations other than an STI clinic (e.g., family physician's office). (Table 4.1)

Table 4.1 Demographic and behavioural characteristics 1143 cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Characteristic	Male	Female	P
	512 (44.8%)	631 (55.2%)	
Age (years)			<0.001
≤19	119 (23.2%)	295 (46.8%)	
20-24	157 (30.7%)	193 (30.63%)	
≥25	236 (46.1%)	142 (22.5%)	
Urban	449 (89.1%)	537 (86.8%)	0.22
Infection type			<0.01
Gonorrhea	308 (60.2%)	325 (51.5%)	
Gonorrhea/chlamydia coinfection	204 (39.8%)	306 (48.5%)	
Provided information on contacts	456 (89.1%)	565 (89.5%)	0.80
Pregnant	--	52 (8.2%)	
Risk factors			
Reported 2 or more contacts	176 (34.4%)	192 (30.4%)	0.16
Same sex partner	45 (8.8%)	5 (0.8%)	<0.001
Unprotected Sex	318 (62.1%)	387 (61.3%)	0.79
Sex trade	15 (2.9%)	28 (4.4%)	0.18
Alcohol and/or drug abuse	69 (13.5%)	75 (11.9%)	0.42
Previous STI	44 (8.6%)	87 (13.8%)	<0.01
Location of initial visit			0.16
STI clinic	189 (37.0%)	208 (33.0%)	
Other	323 (63.1%)	423 (67.3%)	

4.4.2 Repeated gonococcal infection

Of the 1027 unique individuals represented in the dataset, 934 appeared once only, while 93 (9%) had repeat entries (either single infections or coinfections with gonorrhea and chlamydia). These 93 repeaters represented 209 infections, or 18% of the total infections reported during the study period (data not shown). Table 4.2 presents a comparison of repeaters and non-repeaters in the database. Based on unconditional or univariable analysis, repeaters were younger (p=0.001), and were more likely to be coinfected (p=0.001), to have reported 2 or more partners in the last 6 months (p=0.03), to have reported sex trade involvement (either case or contact) (p=0.001), and to have reported alcohol or drug abuse (p=0.02). In the final multivariable model (Table 4.3) being under age 20 (OR 2.3), being coinfected with gonorrhea and chlamydia (OR 1.8), and reporting sex trade involvement (OR 3.6) were associated with identified repeat infection during the 10-year study period.

4.4.3 Coinfection with gonorrhea and chlamydia

Of the 1143 cases of gonorrhea reported between 2003 and 2012, just under half (45%) were coinfected with chlamydia. Table 4.4 presents a comparison of singly infected and coinfected cases in the database. Based on unconditional or univariable analysis, coinfected individuals were younger (p<0.001), and more likely to be female (p<0.01), to have reported 2 or more partners in the last 6 months (p=0.04), and to have reported alcohol or drug abuse (p<0.01). Those who reported a same sex partnership were less likely to be coinfected (p=0.01).

In the final multivariable model (Table 4.5), being under age 25 (OR 2-3.5) and reporting alcohol or drug abuse (OR 1.5) were significantly associated with being coinfected with chlamydia at the time of diagnosis. Reporting a same sex partner was associated with a lower odds (OR 0.5) of being coinfected.

4.5 Discussion

Among our study population, roughly 36% of cases overall (and 46% of female cases) were 19 or under, and 67% were under 25 years of age, at the time of diagnosis, which is reflective of Canadian national data that indicates that the largest proportion of gonorrhea cases is among people under 30 (1). In our dataset, the overall ratio of male cases to female cases was 0.8:1. While Canada's overall male-to-female rate ratio for gonorrhea was 1.3:1.0, our male-to-female case ratio is closer to the rate ratio of 0.7:1.0 reported for the province of Saskatchewan as a

Table 4.2 Unconditional analysis of characteristics at time of first reported diagnosis of individuals with single and repeat infections (n=1027 individuals) from the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

	Non-Repeaters (n=934, 91%)	Repeaters (n=93, 9%)		
	n (%)	n (%)	OR (CI)	P
Age (years)				<0.01
≤19	324 (34.7)	48 (51.6)	2.71 (1.54-4.75)	0.001
20-24	280 (30.1)	27 (29.0)	1.76 (0.95-3.27)	0.07
≥25	329 (35.3)	18 (19.4)	reference category	
Gender				
Male	439 (47.0)	34 (36.8)	reference category	
Female	495 (53.0)	59 (63.4)	1.54 (0.99-2.40)	0.06
Infection				
Gonorrhea	528 (56.5)	36 (38.7)	reference category	
Ct/Gc Coinfection	406 (43.5)	57 (61.3)	2.05 (1.33-3.19)	0.001
Received Correct Treatment				
No	143 (15.31)	10 (10.75)	reference category	
Yes	791 (84.69)	83 (89.25)	1.50 (0.76-3.0)	0.24
Number of Sex Partners in Last 6 months				
1	639 (68.4)	53 (57.0)	reference category	
≥ 2	295 (31.6)	40 (43.0)	1.63 (1.06-2.52)	0.03
*Previous STI				
No	919 (98.4)	93 (100)	reference category	
Yes	15 (1.6)	--	0.47 (0-2.21)	0.27
Sex Trade Involvement				
No	907 (97.1)	84 (90.3)	reference category	
Yes	27 (2.9)	9 (9.7)	3.60 (1.64-7.91)	0.001
Alcohol or Drug Abuse				
No	826 (88.4)	74 (79.6)	reference category	
Yes	108 (11.6)	19 (20.4)	1.96 (1.14-3.38)	0.02
Same Sex Relationship Reported				
No	891 (95.4)	90 (96.8)	reference category	
Yes	43 (4.6)	3 (3.2)	0.69 (0.21-2.27)	0.54
Place of Residence				
Rural	125 (13.6)	6 (6.6)	reference category	
Urban	792 (86.4)	85 (93.4)	2.24 (0.96-5.23)	0.06
Initial Visit Location				
Clinic	325 (34.8)	30 (32.26)	reference category	
Other	609 (65.2)	63 (65.4)	0.89 (0.57-1.40)	0.62

*Previous STI statistics calculated using exact logistic regression.

Table 4.3 Final multivariable model for predictors of repeat infection (n=1005) among cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Variable	OR	P	95% CI
Age (2 df)		0.01	
12-19	2.30	0.01	1.28-4.13
20-24	1.45	0.26	0.76-2.74
25+		Reference category	
Coinfection	1.81	0.01	1.14-2.87
Urban	2.31	0.06	0.98-5.46
Sex trade involvement	3.62	<0.01	1.61-8.15

whole in 2010 (13). The higher rates of infection among women than among men in Saskatchewan is the opposite of those reported by many other jurisdictions, including the United States, Australia, and the United Kingdom (14–16), and implies that female-focused prevention efforts should be considered, especially those aimed at young women, i.e., under 20 years of age.

The finding that 9% of individuals in the database were subsequently reinfected during the 10-year study period is similar to the findings from a 2007 study in Alberta, Canada (17), as well as from a 2009 systematic review of reinfection rates among industrialized nations (18). The association between being under 20 at initial diagnosis and increased risk of reinfection (OR 2.3) also supports previous reports (17–21). Our finding that coinfection at time of initial diagnosis was associated with increased odds (OR 1.8) of repeat infection could indicate that being coinfected is a marker for riskier sexual behaviours, making individuals more susceptible to repeat infection based on sexual network. While the relatively high risk of reinfection in the context of sex trade involvement is not surprising, and has been reported before (20), it does underscore the need to rapidly and appropriately treat individuals reporting such risk factors. Targeted efforts among those at greatest risk, such as follow-up screening and enhanced contact tracing efforts, could reduce the risk and subsequent transmission of reinfection among these risk groups. Current Canadian recommendations include rescreening 6 months after treatment (22); however, for those clients reporting sex trade involvement, or other circumstances where partners are impossible to reach (many are single encounters and unknown by the case),

Table 4.4 Unconditional analysis of characteristics of gonorrhea- and gonorrhea/chlamydia-coinfected cases (n= 1143) reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

	Gonorrhea (n=633, 55%)	Coinfection (n=510, 45%)		
	n (%)	n (%)	OR (CI)	P
Age (years)				<0.001
≤19	169 (26.7)	245 (48.1)	3.67 (2.73-4.94)	<0.001
20-24	193 (30.5)	157 (30.8)	2.06 (1.52-2.80)	<0.001
≥25	271 (42.8)	107 (21.0)	reference category	
Gender				
Male	308 (48.7)	204 (40.0)	reference category	
Female	325 (51.3)	306 (60.0)	1.44 (1.12-1.85)	<0.01
Number of Sex Partners in Last 6 months				
1	446 (70.5)	329 (64.5)	reference category	
≥2	187 (29.5)	181 (45.5)	1.33 (1.02-1.73)	0.04
Previous STI				
No	556 (87.8)	456 (89.4)	reference category	
Yes	77 (12.16)	54 (41.2)	0.78 (0.50-1.22)	0.28
Sex Trade Involvement				
No	611 (96.5)	489 (95.9)	reference category	
Yes	22 (3.5)	21 (4.1)	1.20 (0.63-2.29)	0.6
Alcohol or Drug Abuse				
No	570 (90.1)	429 (84.1)	reference category	
Yes	63 (10.0)	81 (15.9)	1.72 (1.19-2.47)	<0.01
Same Sex Relationship Reported				
No	596 (94.2)	497 (97.5)	reference category	
Yes	37 (5.9)	13 (2.6)	0.41 (0.21-0.81)	0.01
Place of Residence				
Rural	71 (11.5)	66 (13.20)	reference category	
Urban	552 (88.6)	434 (86.8)	0.84 (0.57-1.22)	0.36

Table 4.5 Final multivariable model for predictors of coinfection with gonorrhea and chlamydia (n=1140) among cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Variable	OR	P	95% CI
Age (2 df)		<0.001	
12-19	3.52	<0.001	2.61-4.75
20-24	2.02	<0.001	1.48-2.75
25+		Reference category	
Alcohol and/or drug abuse	1.48	0.04	1.02-2.13
Same sex partner	0.52	0.05	0.27-1.00
ICC for patient ID:		*4.5081E-12*	

expedited partner therapy (EPT)—whereby a case is given medication to provide directly to his/her partner(s)—could provide an effective approach to reducing the risk of reinfection from an untreated partner (23). The Centers for Disease Control and Prevention in the United States recommend EPT as an effective partner management strategy (24); it is currently not an implemented policy in RQHR.

It is not surprising that a large proportion of our sample population was coinfected with both gonorrhea and chlamydia; this supports the findings of previous North American studies (25,26) and Canadian national guidelines that gonorrhea should be treated with combination therapy (ceftriaxone or cefixime with azithromycin) to target both infections (22). Our finding that individuals under age 25 had increased odds of coinfection (OR 2-3.5) also supports previous research (25–27) and could be a related to the fact that younger women are thought to be more susceptible to chlamydia than are older women, due to increased cervical ectopy (28). This could also account for younger males being more likely to be coinfected, if the local sexual networks exhibit age homogeneity, as implied by our finding that the mean age difference between cases and their contacts was just four years. The increased odds of coinfection among those who reported alcohol or drug abuse does not have a plausible biological explanation. However, it could be a marker for sexual network, indicating that coinfection is more prevalent in networks of individuals with higher risk behaviors, such as alcohol or drug abuse.

Last, the apparent protective influence of having reported a same sex partnership on the risk of coinfection is also not clearly related to any biologically plausible phenomenon, although it has

been reported previously (29). It is possible that this association could result from memberships in sexual networks in which chlamydia infections are less common.

Low positive response rates for some risk factors, including sex trade involvement and a history of same sex partners, could have limited the power to evaluate the effect of these factors on the outcomes of interest. Also, because this study used previously-collected information from notifiable disease files, the collection of risk factor and other information from patients was not standardized. A large number of health care workers from different facilities recorded data over the study period. Different approaches could have affected the amount or quality of information gathered from patients presenting at different times and different facilities. Also, potential movement from one health region to another could have limited our ability to identify repeat infections over the study period, as could asymptomatic or other undiagnosed infection. Finally, potentially stigmatizing behaviors, including alcohol and drug use or purchasing commercial sex, could have been under- or misreported (30).

We were able to identify several factors associated with increased risk of reinfection and coinfection with gonorrhea and chlamydia among STI patients in RQHR, and our findings are directly relevant to prevention and control efforts in the region—and, potentially, in other Saskatchewan health regions with larger urban centres. Because the risk of reinfection is heightened among those individuals who are under 20 years of age, who are coinfected, or who report sex trade involvement for themselves or their partners, health care workers in RQHR could use this information to guide their counselling and treatment choices. Targeted counselling efforts focused on those at high risk of reinfection could have an effect on reinfection rates; however, factors beyond the control of the individual, such as external pressures and group norms, will likely still play a strong role in influencing choices. Treatment protocols could have a great effect. For example, EPT might be an appropriate choice for clients with these risk factors to prevent potential reinfection from untreated partners (23). Similarly, clients who are under 25 or report alcohol or drug abuse could be good candidates for presumptive dual therapy, given the increased odds of coinfection among this demographic. Additionally, regular review of some of the parameters identified here to be associated with reinfection and coinfection could assist in measurement of STI intervention effectiveness in RQHR.

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CHAPTER 5: ASSESSMENT OF THE UTILITY OF SOCIAL NETWORK ANALYSIS FOR THE CONTROL OF BACTERIAL SEXUALLY TRANSMITTED INFECTIONS IN SASKATCHEWAN

(unpublished)

As in China, rates of gonorrhea remain high in Saskatchewan. In contrast to China, levels of antimicrobial resistance are currently low. High rates of disease in the province do indicate, however, that the current approach to disease control is not effective. Novel methods are warranted to better understand and control transmission, especially before AMR becomes established in the province. Social network analysis is a powerful tool, which has been demonstrated to provide a significant contribution to the understanding of STI transmission dynamics in many jurisdictions. It was hypothesized that a SNA approach would provide additional information related to the transmission of gonorrhea in the Regina Qu'Appelle Health Region, which could better position policy makers to both control disease and be proactive in delaying AMR emergence. Unfortunately, the current system of data collection and storage in Saskatchewan largely limited the utility of an otherwise powerful approach.

5.1 Introduction

In spite of declining during the early 1990s, rates of bacterial STIs have been increasing in Canada since 1999. Data from 2011 indicate that Saskatchewan's gonorrhea rate of 71.7 per 100,000 is second only to that of Manitoba, among the Canadian provinces, and more than twice the rate of Ontario, Quebec, and Canada as a whole (1). The very real potential of multi-drug resistant, untreatable gonorrhea (2), coupled with the synergistic relationship between *Neisseria gonorrhoeae* and HIV (3), make it imperative that gonorrhea control efforts are improved and transmission of disease reduced. Improved understanding of transmission dynamics, along with evaluation of systems and tools currently in place to address disease transmission, are of utmost importance to address the growing burden of disease in the province.

Information routinely collected on STI cases and contacts forms the basis from which sexual networks can be described, making social network analysis (SNA) a potentially powerful tool for understanding transmission dynamics and appropriate control efforts for STIs. SNA has been applied to gonorrhea in various settings (4) including Colorado Springs (5,6), San Francisco (7), the United Kingdom (8–12), Manitoba (6,13–17), and Alberta (18). Such studies demonstrate that SNA provides a powerful tool to enhance our understanding of disease transmission dynamics, potentially offering new information relevant to targeted control efforts. For example, network studies have enhanced understanding of core groups and network members (13–15), been applied to determining the epidemic phase of STIs in a given population (5–7), been used to illustrate the importance of location in disease transmission (18), enabled researchers to identify geographic bridges for disease transmission (14), and been combined with molecular techniques to support the strength of SNA methods (8,9,11-17). The objectives of the study presented here were to evaluate the potential contribution of SNA to improve understanding of gonorrhea transmission in Saskatchewan.

Data on all cases of gonorrhea recorded in the Regina Qu'Appelle Health Region (RQHR) from 2003 to 2012 were included. RQHR is located in south-central Saskatchewan and serves 260,000 residents, including those of Saskatchewan's capital city, Regina. It is the second largest health region in Saskatchewan, and has recorded an average of 100 cases of gonorrhea and 1000 cases of chlamydia each year since 2008. This study builds on my previously published epidemiologic study (Chapter 4) using the same dataset, and was designed to determine the potential of SNA to

enhance understanding of gonorrhea transmission dynamics in this population (19). It is the first study of SNA as applied to gonorrhea transmission in Canada outside of the provinces of Alberta or Manitoba.

5.2 Methods

5.2.1 Sample

In Saskatchewan, Regional Health Authorities send specimens for testing to the Saskatchewan Disease Control laboratory (SDCL); all confirmed gonorrhea cases are reported to the appropriate public health authorities. In accordance with national guidelines, contact tracing is initiated in the event of a positive laboratory diagnosis, and includes individuals who were contacts within 60 days prior to the test date. Contact tracing, which is triggered by the notification being filed, is generally done by public health staff in the case's home health region. If a contact resides in a different health region, a referral is made and follow-up is the responsibility of public health staff in that region. We accessed the notifiable STI files within the RQHR and extracted the records for all laboratory confirmed gonorrhea cases—including those concurrently infected with chlamydia—from January 1, 2003 to December 31, 2012. This study was approved by the research ethics boards of both the University of Saskatchewan and the RQHR (no. 12-323 and 12-98, respectively).

In the RQHR, the majority of diagnostic tests for gonorrhea currently use urine-based nucleic acid amplification (NAAT). Antimicrobial susceptibility testing is carried out on cultured samples, but cultures are rarely performed, in spite of being recommended by the Saskatchewan Ministry of Health (20). Every positive gonorrhea case recorded in RQHR over this time period was included in the dataset. The RQHR files contained demographic information including name, health services number (HSN), age, date of birth, and address; event-related information including diagnosing facility, laboratory tests reported, and type and date of treatment; and, risk factor information including sexual history, drug and alcohol use, and number of partners. Information on sexual contacts and their follow-up was also recorded. All contacts who presented and had a laboratory-confirmed infection were also included in the extracted list of gonorrhea cases.

5.2.2 Data management and analysis

Microsoft Access (21) was used to create a relational database that preserved the linkage between cases and their named contacts. To maintain security and confidentiality of client files, all data abstraction and initial processing was done on-site at health region offices. Original files were in hardcopy format for the first eight years of the study period. Prior to any information being moved off site, all personal identifiers including last name and address were removed. An algorithm was applied to scramble and anonymize clients' HSNs while preserving the ability to recognize repeat occurrences of disease in individuals during the 10 year study period.

After the data were de-identified, descriptive analyses were carried out using Microsoft Excel (22) and Stata IC/12.1 (23). Age was categorized prior to analysis. For the purpose of this analysis, we defined "repeater" as someone who appeared two or more times in the 10-year database. For repeat infections occurring at intervals of 2 months or less, we verified that appropriate, observed therapy (dual azithromycin and cefixime) was administered for the prior infection, to rule out persistent infection instead of repeat infection. Because Saskatchewan has extremely low levels of antibiotic resistance (24), treatment failure was considered unlikely.

5.2.3 Social network analysis

The database was stratified by year to allow for the creation of sexual network maps for each of the 10 years of data. The file for each year included all cases diagnosed in that calendar year, as well as any named contacts reported by each case at that visit (even if the contact occurred previous to that calendar year). A freeware program called "createpajek" (http://vlado.fmf.uni-lj.si/pub/networks/pajek/howto/excel2Pajek.htm) was used to convert long format Excel files to a format that can be read by both Pajek (25) and NetDraw (26). The resulting files were then used to create network maps and calculate measures including network density, component size, and degree, for each year. Density measures the total number of connections in a network divided by the total possible number of connections (27); a very dense network is one in which many nodes are connected to one another. A component is a subgroup in a network in which all nodes are connected by at least one tie (27), and component size refers to the total number of nodes in the given component. Degree indicates the total number of connections a node has (27); in this case, degree represents the number of sexual contacts reported by the node, or who named that node.

A network map was also created and the same measures calculated considering the entire 10-year period, reflecting all cases presenting during the 10 year period, and a summary of their contact history as reported at each visit. For example, if a case presented for testing and treatment in 2005 and reported 3 distinct contacts, and in 2007 and reported 2 more distinct contacts, the case was included once, and all 5 contacts reported were included as linked to that case.

5.2.4 Statistical modeling

The data included in this analysis were previously analyzed to identify socio-demographic characteristics associated with repeated gonorrhea and coinfection with gonorrhea and chlamydia (Chapter 4) (19). The data were reanalyzed here to identify any potential benefit associated with the addition of network position measures to the previously described risk factors, and to identify the potential advantages of using a SNA approach in addition to traditional epidemiologic data analysis. Prior to multivariable model building, observations for two cases with outlying ages (< 6 months and >75 years) were dropped.

The unconditional association between each SNA measure and both repeated gonorrhea and coinfection with gonorrhea and chlamydia were examined to identify potentially useful predictors of infection status. All SNA measures were linear in the logit, and were included as continuous variables for the analysis of repeat infections. For the coinfection outcome, degree was not linearly associated with the logit and was categorized before analysis. For SNA measures based on the 10-year network, degree and component size were included as continuous variables for the repeater and coinfection outcomes, respectively; all others were categorized.

A multivariable logistic regression model was built to identify factors associated with having repeat entries in the database, using one entry per person, based on characteristics at first entry and controlling for amount of follow-up time.

To identify variables associated with being coinfected with gonorrhea and chlamydia at the time of visit, a mixed-effects multivariable logistic regression model was built using a random intercept to account for clustering by participant identification (anonymized HSN) due to repeat entries.

Starting with the risk factors identified from the multivariable analysis in the previous study (19), the SNA measures found to be unconditionally associated with the outcome (at $p \leq 0.2$), were

added to the model. Final models were developed using manual backwards elimination. Likelihood ratio tests and comparison of Akaike Information Criteria (AIC) were used to select nested and non-nested models, respectively. Only significant independent risk factors ($p<0.05$) and important confounders were retained in the final multivariable model for each outcome. Confounding was recognized when the difference between crude odds ratio for a risk factor-outcome association of interest and the same odds ratio adjusted for the potential confounder was > 10%. After establishing main effects models for each outcome, all possible two-way interactions were considered; only interactions significant at $p<0.05$ were retained in the final models.

The Intraclass Correlation Coefficient (ICC) was estimated as σ^2patientID / (σ^2patientID + $\pi^2/3$) for the final coinfection model (28). Potential collinearity of SNA measures was tested using Spearman's Rho; variables shown to be correlated were not considered eligible for the same model. Residual plots were examined for each model to check for outliers.

5.3 Results

There were 1143 occurrences of laboratory confirmed gonorrhea in the health region from 2003-2012, representing 1027 unique individuals. Of these 1143 cases, only 126 (11%) had cultures taken at the clinical visit. From these 1143 case visits, 1524 contacts were elicited, representing 1383 unique individuals. Table *5.*1 shows the frequency of reporting 0-10 partners in any given visit, as well as over the 10 year period. The average number of contacts reported *by an individual* in any one year was 1.3 (range 0-7) and over the 10-year period it was 1.6 (range 0-10). Just over half of cases (55.2%) were female, and just under half (44.2%) were coinfected with chlamydia at the time of diagnosis (19). Three cases had missing data for the year of infection, and were therefore not included in the SNA by year.

5.3.1 Network characteristics

Visualization of the network for each year revealed a combination of linear and radial components. None of the linear components included cycles, which are closed structures or "loops" in the network, whereby the path of sexual connections circles back upon itself. The final year of the dataset, 2012, included the greatest amount of nodes (304) and the largest component (12) (Figure 5.1a). In contrast, in 2009 there were only 156 nodes and the largest

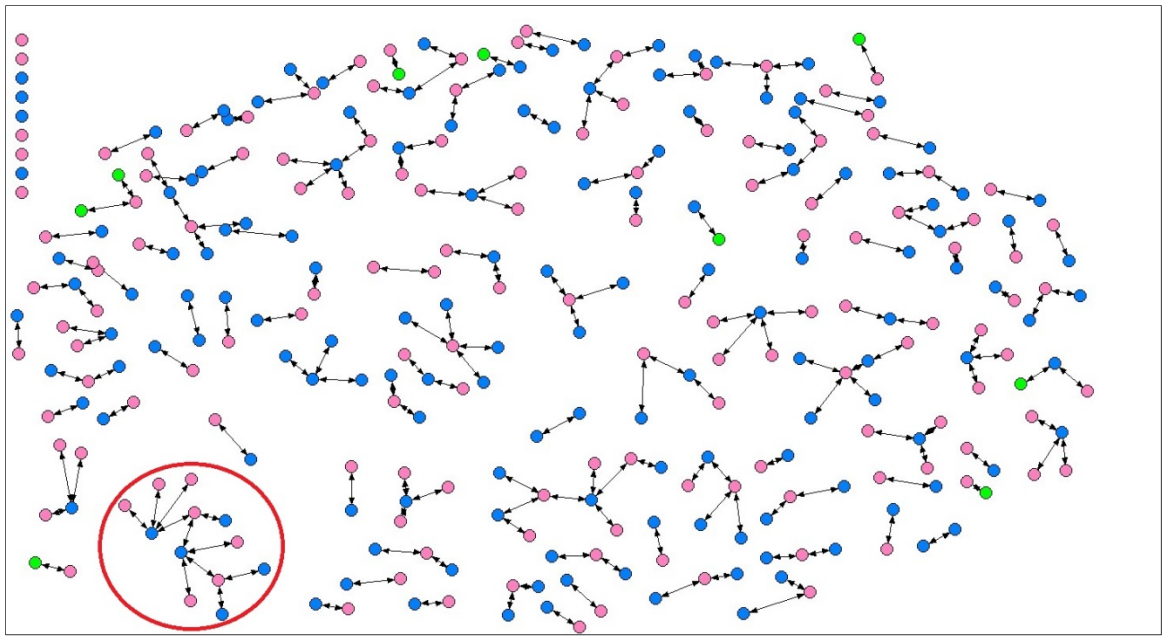
Table 5.1 Frequency of cases in the notifiable STI files in the Regina Qu'Appelle Health Region reporting 0-10 partners, in a single visit, and over the 10-year period (2003-2012)

Number of Contacts Reported	1 visit (n)	10 years (n)
0	122	112
1	670	572
2	250	282
3	70	95
4	19	40
5	6	13
6	4	12
7	2	7
8	0	4
9	0	0
10	0	6

component contained only 6 individuals (Figure 5.1b). Table 5.2 shows the network characteristics by year. Network density remained relatively similar throughout the 10 years, indicating a considerably fragmented network. The proportion of the network made up of isolates (individuals with no observed connections to others) declined throughout the 10 years, while the proportion comprised of triads or larger groups varied substantially over time, with no discernible pattern (Figure 5.2). Median degree and median component size remained relatively stable over the 10-year span.

When all 10 years of data were considered together, the largest component included 49 individuals. The median component size was 3 (IQR=2) and the median degree was 1 (IQR=1). Both degree and component size measures calculated based on the 10-year network were positively associated with repeat infection ($p<0.001$) and coinfection ($p<0.01$) in unconditional analysis. (Data not shown)

a.



b.

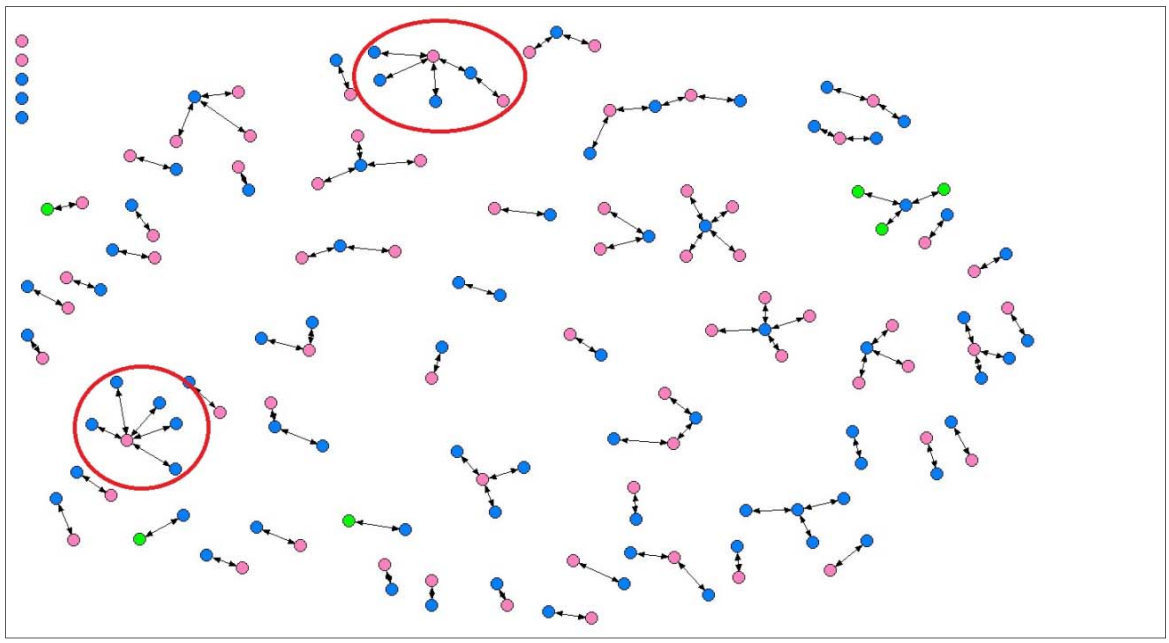


Figure 5.1 Network maps from gonorrhea cases and their reported contacts in the Regina Qu'Appelle Health Region for 2012 (a) and 2009 (b).

Blue nodes are those recorded males, pink nodes are those recorded as females, and green nodes are unknown gender. Red circles indicate the largest component(s) for each year.

Table 5.2 Gonorrhea sexual network characteristics in Regina Qu'Appelle Health Region, from 2003-2012

				Proportion of the network comprised of:						
Year	Total nodes	Presented n (%)	Density	Isolates n (%)	Dyads n (%)	Triads n (%)	Larger n (%)	Largest component	Median component size (IQR)	Median degree (IQR)
2003	199	105 (52.7)	0.006	18 (9.0)	74 (37.2)	60 (30.2)	47 (23.6)	10	3 (1)	1 (0)
2004	235	129 (54.8)	0.005	20 (8.5)	96 (40.9)	72 (30.6)	47 (20.0)	8	3 (1)	1 (0)
2005	227	111 (48.9)	0.006	15 (6.6)	86 (37.9)	51 (22.5)	75 (33.0)	11	3 (2)	1 (0)
2006	235	106 (45.1)	0.006	10 (4.3)	78 (33.2)	63 (26.8)	84 (35.7)	7	3 (2)	1 (0)
2007	180	87 (48.3)	0.008	8 (4.4)	66 (36.7)	54 (30.0)	52 (28.9)	10	3 (2)	1 (0)
2008	209	102 (48.8)	0.006	11 (5.3)	94 (45.0)	72 (34.4)	32 (15.3)	6	2 (1)	1 (0)
2009	156	69 (44.2)	0.008	5 (3.2)	68 (43.6)	24 (15.4)	59 (37.8)	6	3 (2)	1 (0)
2010	243	121 (49.8)	0.006	6 (2.5)	118 (48.6)	45 (18.5)	74 (30.5)	7	2 (2)	1 (0)
2011	302	139 (46.0)	0.004	7 (2.3)	122 (40.4)	99 (32.8)	74 (24.5)	7	3 (1)	1 (0)
2012	304	144 (47.4)	0.005	9 (3.0)	116 (38.2)	69 (22.7)	110 (36.2)	12	3 (2)	1 (0)

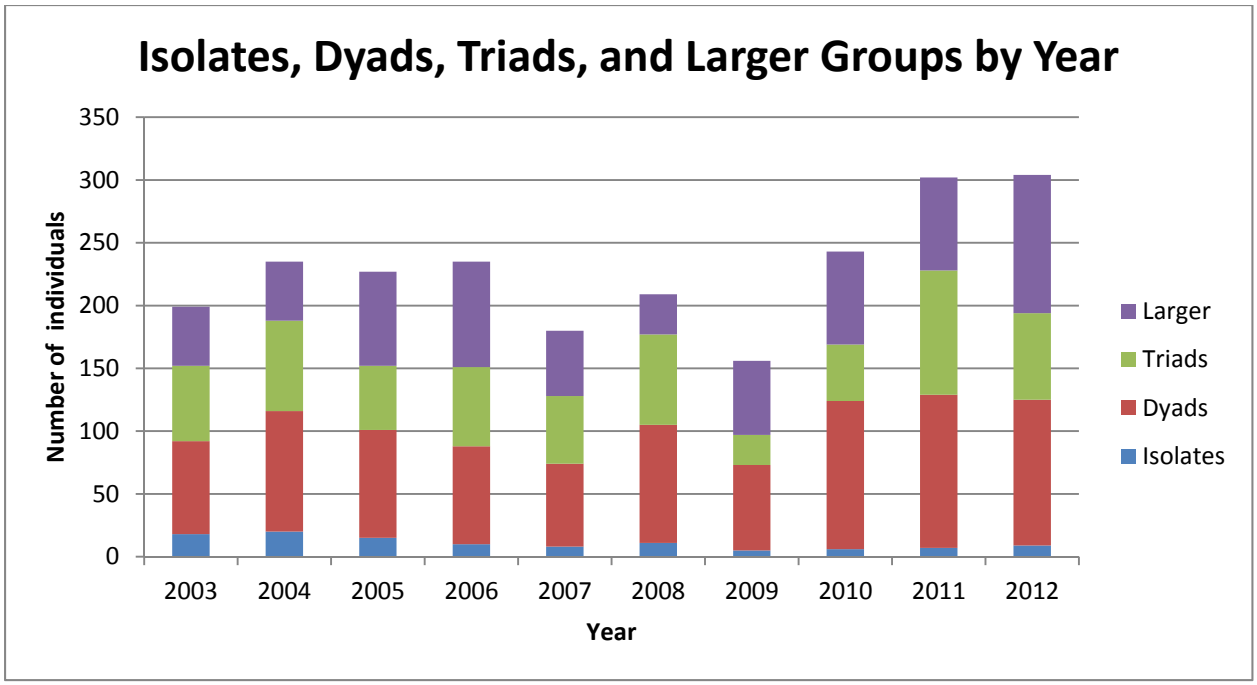


Figure 5.2 Proportion the of the Regina Qu'Appelle gonorrhea sexual network comprised of isolates, dyads, triads, and larger components, by year, 2003-2012

5.3.2 Coinfection with chlamydia

In the unconditional analysis, increases in component size and degree were associated with increasing odds of being coinfected with chlamydia (Table 5.3). After accounting for risks associated with previously identified sociodemographic variables, only component size was associated with being coinfected with chlamydia (OR 1.10) (Table 5.4). For each additional person in a component, any member of the component had a 10% greater chance of being coinfected, after accounting for all other risk factors. Previously identified risk factors that remained significant in the model after accounting for connectivity measures included age and same sex partnerships. Being under 25 was positively associated with being coinfected with chlamydia (OR 2-3.4). In contrast, reporting a same sex partnership was associated with decreased odds (OR 0.5) of being coinfected; the SNA measures examined in this study did not confound these associations. The previously identified association between reporting alcohol or drug abuse to being coinfected was not significant after accounting for component size.

Table 5.3 Unconditional analysis of the relationship of SNA measures to coinfection status, among cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Variable	OR	P	95% CI
Degree		0.002	
0	1.21	0.40	0.78-1.87
1		Reference category	
2 or higher	1.64	0.001	1.24-2.17
Component Size	1.17	<0.001	1.09-1.26

Table 5.4 Multivariable model for risk factors related to coinfection status among cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Variable	OR	P	95% CI
Age (2 df)		<0.001	
Age 12-19	3.29	<0.001	2.43-4.47
Age 20-24	1.96	<0.001	1.44-2.68
Age 25 +		Reference category	
Same sex partner	0.50	0.04	0.26-0.96
Component Size	1.10	<0.01	1.03-1.18
ICC:		*1.29E-10*	

5.3.3 Repeat infection

Increasing values of component size and degree were also associated with increasing odds of repeat infection in the unconditional analysis (Table 5.5). After multivariable analysis, in addition to those variables identified in the previous study (17), degree was significantly associated with the outcome (OR 1.3, $p<0.1$) (Table 5.6). This association indicates that for every additional contact, odds of repeat infection were 30% higher, after accounting for all other risk factors. When component size was included in the final model, in place of degree, the associations between the other variables and the outcomes were not significantly changed. In this model, component size is shown to be positively associated with repeat infection (OR 1.14, $p<0.01$), although the relationship is not quite as strong as between degree and the outcome. The model using degree was chosen as the final model based on its slightly lower AIC.

Table 5.5 Unconditional analysis of the relationship of SNA measures to repeat infection among cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Variable	OR	P	95% CI
Degree	1.40	<0.01	1.16-1.69
Component size	1.20	<0.01	1.17-1.58

Table 5.6 Multivariable model for risk factors related to repeat infection among cases of gonorrhea reported to the Regina Qu'Appelle Health Region's notifiable STI files from 2003-2012

Variable	OR	P	95% CI
Age (2 df)		0.02	
12-19	2.22	<0.01	1.23-4.01
20-24	1.39	0.30	0.73-2.63
25+	Reference category		
Coinfection	1.73	0.02	1.09-2.75
Urban	2.22	0.07	0.94-5.27
Sex trade involvement	3.54	<0.01	1.55-8.06
Degree	1.32	<0.01	1.08-1.61

5.4 Discussion

Gonorrhea has been a nationally notifiable disease in Canada since 1924 (29). The requirement to report gonorrhea, as well as to follow-up with contact tracing efforts for any person exposed within the preceding 60 days, results in a wealth of information related to gonorrhea in the Canadian population. In spite of the amount of information collected, and the extremely high rates of infection in Saskatchewan, to date only two epidemiologic studies of gonorrhea in Saskatchewan have been published (19,30). The goal of the present study was to evaluate the potential value of SNA, a tool that has been successfully applied to STIs in a wide variety of settings, in a province where disease rates remain incredibly high, and additional options are needed for disease control. This is the first study to apply SNA techniques to STI transmission in Saskatchewan.

Social network analysis of the data collected in the health region over the 10-year period examined in this study suggested that the sexual network was substantially fragmented. This type

of fragmentation indicates that there are many fewer connections in the network than are possible for the given number of nodes, and has been seen in previous SNA studies of gonorrhea and chlamydia in the United States (5,7). The mean component sizes of between 2.7 and 3.5 are also similar to what has been reported in previous contact tracing studies (5,6,9,10,14,18). Potterat et al. (5) argue that fragmented networks comprised of relatively small, acyclic components (e.g., those that do not circle back upon themselves) indicate endemic, rather than epidemic disease spread. Further, they suggest that such networks are better suited to targeted screening than contact tracing, which is the current approach in Saskatchewan. However, it seems plausible that the lack of connectivity could also represent limitations of contact tracing in elucidating a complete network, especially given the jurisdictional boundaries of contact tracing and data storage, discussed below.

Our finding that in the presence of the component size variable, the previously identified relationship between alcohol/drug abuse and coinfection disappeared could support the interpretation that the association was a marker for membership in high risk sexual networks (19). It is plausible that increasing component size is associated with increasing participation in other high risk behaviors. The association between increasing component size and risk of coinfection in the present study was not surprising. Potterat et al. (5) found that coinfected (gonorrhea/chlamydia) cases were disproportionately represented in larger components in their 2002 Colorado Spring study. Additionally, they found that cases with repeat chlamydia infection were also more common in larger components, similar to our findings of degree or component size being associated with repeat gonorrhea. While the Colorado Springs study was substantially larger than ours, with a study population of 9114 over the 4-year study period compared to our 304 in the largest single year (2012), we were able to distinguish similar associations between specific SNA measures and likelihood of repeat or coinfection.

While SNA has been successfully applied in various other jurisdictions, there are several factors at work in Saskatchewan that hinder the utility of an otherwise powerful tool like SNA. Firstly, in comparison to centralized STI control programs in other areas, Saskatchewan's data are collected and stored individually by each of the province's 13 regional health authorities. Therefore, should an individual who tests positive for gonorrhea in one health region report a contact who lives in another, the follow-up is referred to the second health region, and the

resultant information effectively lost to the original health region's database. Similarly, if a case or contact is eligible to receive services through Health Canada's First Nations and Inuit Health Branch (FNIHB), the follow-up is carried out and information stored by that agency. It is a centralized system like Manitoba's that allowed Wylie and Jolly (14) to reveal geographic bridges for chlamydia and gonorrhea infection transmission spanning a vast area of that province, from Winnipeg to northern Manitoba. Because of the number of jurisdictions involved in the collection and storage of STI data, such geographic bridging would be difficult to impossible to uncover when data are managed by smaller, individual health authorities as in Saskatchewan, and the size of the network that can be described from any one region's STI data is considerably limited.

Combining molecular and social network data for analysis has also been shown to enhance the analytic power of SNA for control of STIs in the United Kingdom (8,9,11,12). As well, researchers in Canada have demonstrated the power of such a combined approach as applied to a tuberculosis outbreak in British Columbia (31), and STI control in Manitoba (16,17).

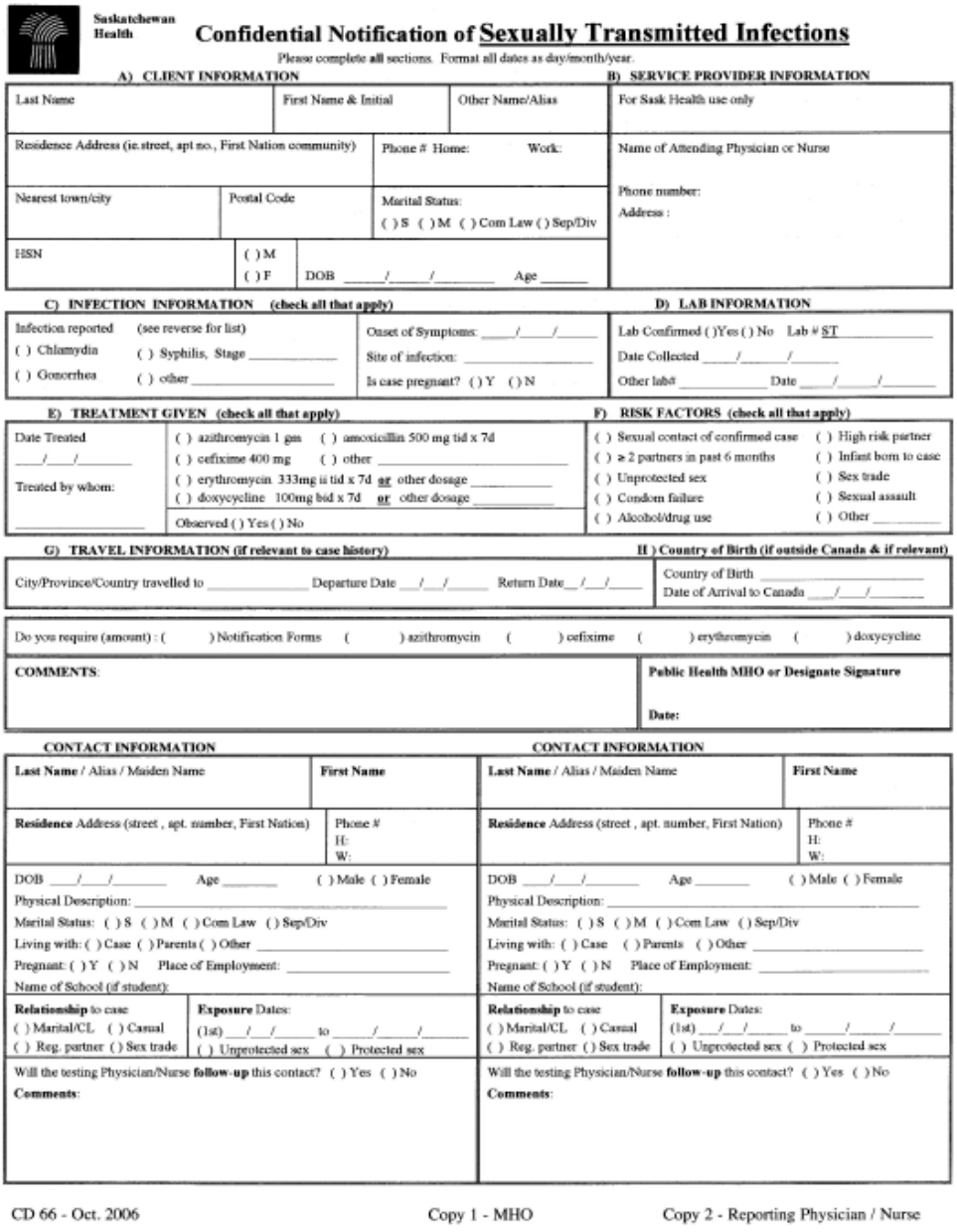
Given the highly fragmented nature of the networks we were able to uncover in this study, it is possible that the addition of molecular data could have increased the utility of an SNA approach to understanding transmission in RQHR. For example, even if individuals or components appear unconnected based on their first-person reports of sex partnerships, the molecular network might imply otherwise. While two people infected with the same strain of gonorrhea are not necessarily sex partners, it does imply a potential network connection. Previous research involving molecular analysis of *N. gonorrhoeae* isolates from Saskatchewan, through DNA sequencing of both specific loci and whole genomes, has revealed a substantial amount of information on the distribution and population structure of *N. gonorrhoeae* in the province (32,33), and indicates that strains have spread throughout the province over time. Although molecular analysis was carried out on isolates collected during the same study period, strain type information was available for only 53 (<5%) of the RQHR cases in the current study. The very small number of samples in this study that had available molecular strain typing data precluded the possibility of leveraging molecular data to improve our understanding of the networks in RQHR. A more proactive approach toward the collection of molecular data, perhaps by making molecular

analysis of positive samples a standard procedure, could contribute substantially toward improving the potential for SNA to analyze gonorrhea transmission in the province.

Other serious limitations inherent in the Saskatchewan system are related to the way data are collected. For example, the STI notification form (Figure 5.3), required by law to be filled out for all laboratory-confirmed positive gonorrhea cases, provides space for listing the information for two contacts, with instructions to use additional forms if necessary to include more contact information. Anecdotal reports from STI clinic staff indicate that this likely limits the extent to which physicians may attempt to elicit contacts from a case; when two names are given, the interview may be considered complete. Research into whether a change in the way contacts are elicited and recorded resulted in a general increase in contacts named could determine the extent to which the current form may be contributing to our limited ability to uncover the network at risk.

Additionally, because there are a variety of locations at which STI testing and diagnosis are carried out, there is a similar variety in the level of rigor with which client interviews are carried out. The notifiable STI form includes checkboxes for various risk factors (e.g., drug and alcohol use, multiple partnerships, same sex partnerships, sex trade work, etc.); many physicians, however, generally do not check these boxes, leaving it difficult to determine whether the boxes are unchecked because there are no relevant risk factors, or because the interview did not cover the topic. The addition of a checkbox indicating that the questions were or were not asked, generally, could improve understanding of the strength of risk factor data as indicated on the form.

Further, because filling out the notifiable STI form is triggered by receiving a positive lab result (typically a few days after the physician or clinic visit), it may not be practical or possible to gather all the required information, and many of the forms are incomplete. Additionally, the contact notification forms are received by public health, and contact tracing initiated, after the positive test has been received and notifiable STI form filed, delaying the initiation of contact tracing efforts potentially by several days. Such a delay not only increases the likelihood of exposed individuals continuing to transmit infections, but also may limit the extent of the network that can be identified, as it can be challenging to locate the index case for follow-up several days after the initial visit and testing.



Saskatchewan Health

Confidential Notification of Sexually Transmitted Infections

Please complete **all** sections. Format all dates as day/month/year.

A) CLIENT INFORMATION

Last Name	First Name & Initial	Other Name/Alias
Residence Address (ie.street, apt no., First Nation community)	Phone # Home: Work:	
Nearest town/city	Postal Code	Marital Status: ( ) S ( ) M ( ) Com Law ( ) Sep/Div
HSN	( ) M ( ) F	DOB ____/____/____ Age ____

B) SERVICE PROVIDER INFORMATION

For Sask Health use only

Name of Attending Physician or Nurse

Phone number:

Address :

C) INFECTION INFORMATION (check all that apply)

Infection reported (see reverse for list)

( ) Chlamydia ( ) Syphilis, Stage ____

( ) Gonorrhea ( ) other ____

Onset of Symptoms: ____/____/____

Site of infection: ____

Is case pregnant? ( ) Y ( ) N

D) LAB INFORMATION

Lab Confirmed ( )Yes ( ) No Lab # ST____

Date Collected ____/____/____

Other lab# ____ Date ____/____/____

E) TREATMENT GIVEN (check all that apply)

Date Treated ____/____/____

Treated by whom: ____

( ) azithromycin 1 gm ( ) amoxicillin 500 mg tid x 7d

( ) cefixime 400 mg ( ) other ____

( ) erythromycin 333mg ii tid x 7d or other dosage ____

( ) doxycycline 100mg bid x 7d or other dosage ____

Observed ( ) Yes ( ) No

F) RISK FACTORS (check all that apply)

( ) Sexual contact of confirmed case ( ) High risk partner

( ) ≥ 2 partners in past 6 months ( ) Infant born to case

( ) Unprotected sex ( ) Sex trade

( ) Condom failure ( ) Sexual assault

( ) Alcohol/drug use ( ) Other ____

G) TRAVEL INFORMATION (if relevant to case history)

City/Province/Country travelled to ____ Departure Date __/__/____ Return Date__/__/____

H) Country of Birth (if outside Canada & if relevant)

Country of Birth ____

Date of Arrival to Canada ____/____/____

Do you require (amount) : ( ) Notification Forms ( ) azithromycin ( ) cefixime ( ) erythromycin ( ) doxycycline

COMMENTS:

Public Health MHO or Designate Signature

Date:

CONTACT INFORMATION

Last Name / Alias / Maiden Name	**First Name**
Residence Address (street , apt. number, First Nation)	Phone # H: W:

DOB ____/____/____ Age ____ ( ) Male ( ) Female

Physical Description: ____

Marital Status: ( ) S ( ) M ( ) Com Law ( ) Sep/Div

Living with: ( ) Case ( ) Parents ( ) Other ____

Pregnant: ( ) Y ( ) N Place of Employment: ____

Name of School (if student):

Relationship to case	**Exposure** Dates:
( ) Marital/CL ( ) Casual ( ) Reg. partner ( ) Sex trade	(1st) __/__/____ to ____/____/____ ( ) Unprotected sex ( ) Protected sex

Will the testing Physician/Nurse **follow-up** this contact? ( ) Yes ( ) No

Comments:

CONTACT INFORMATION

Last Name / Alias / Maiden Name	**First Name**
Residence Address (street , apt. number, First Nation)	Phone # H: W:

DOB ____/____/____ Age ____ ( ) Male ( ) Female

Physical Description: ____

Marital Status: ( ) S ( ) M ( ) Com Law ( ) Sep/Div

Living with: ( ) Case ( ) Parents ( ) Other ____

Pregnant: ( ) Y ( ) N Place of Employment: ____

Name of School (if student):

Relationship to case	**Exposure** Dates:
( ) Marital/CL ( ) Casual ( ) Reg. partner ( ) Sex trade	(1st) __/__/____ to ____/____/____ ( ) Unprotected sex ( ) Protected sex

Will the testing Physician/Nurse **follow-up** this contact? ( ) Yes ( ) No

Comments:

CD 66 - Oct. 2006 Copy 1 - MHO Copy 2 - Reporting Physician / Nurse

Figure 5.3 STI Notification form used in Saskatchewan during study period (2003-2012)

Perhaps the biggest limitation is the complicated system of jurisdictional data collection and storage. Further, while connections between the two major centres (Saskatoon and Regina), rural and urban areas, and the urban centres and First Nation reserves almost certainly exist, it was not possible to demonstrate such connections using the available data. Access to a centralized

information system reflecting a more complete history of client contacts would provide enhanced ability to identify relationships between network positions and outcomes of interest for disease control, as well as potentially reveal important connections between distant communities in the province. However, under the current system of data collection and storage, SNA studies of STI transmission in Saskatchewan will remain seriously limited.

Reporting STIs such as gonorrhea is mandated by law, and such reporting necessarily results in the collection and storage of a substantial amount of sociodemographic and sexual history data. Unfortunately, as demonstrated here, the application of powerful analytical techniques, which could greatly improve our understanding of the transmission of gonorrhea is markedly hindered. The limited applicability of such a wealth of data that exists across the province, beyond simple contact notification, raises ethical questions about the collection of such data. It is important to consider the intention of the mandate to report notifiable diseases. Notifiable diseases have been identified as priority areas for monitoring and control efforts, which is why the requirements for reporting and contact tracing exist. However, if the current state of the system prevents the data collected from being used to its full potential in terms of enhancing control efforts, should it be collected at all? Currently, the only use of the data collected is to follow up and treat cases and contacts. Rates of gonorrhea remain very high, indicating this cycle of identifying and treating cases and contacts alone may be insufficient to effectively control disease transmission. Improvements could potentially be made if the data were robust enough to inform the development of innovative and effective interventions.

The system-related limitations discussed herein provide a basis from which to begin to consider possible improvements to better aide health professionals in effectively combating gonorrhea and other STIs. In a province with one of the highest gonorrhea rates in the country, improvements in disease control are desperately needed. The mandate to report a disease, and even to carry out contact tracing efforts, is clearly not enough when the system is so fragmented. In its current state, the STI control system in Saskatchewan greatly limits the application of proven analytical techniques to the control of disease transmission. Under these circumstances, the application of SNA to gonorrhea transmission in Saskatchewan is unlikely to provide any information for meaningful improvements in disease control.

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CHAPTER 6: PREDICTING THE EFFECTS OF EMERGING ANTIMICROBIAL RESISTANCE IN *N. GONORRHOEAE* IN SASKATCHEWAN USING DYNAMIC SIMULATION MODELING

(unpublished)

Several chapters in this thesis illustrated that client attributes can be useful for clinicians to tailor approaches with patients to support more effective overall disease control—both in China, where both gonorrhea and AMR rates are high, and in Saskatchewan, where gonorrhea rates are high, yet AMR is low. This chapter focuses on the exploration, through dynamic simulation modeling, of scenarios related to the emergence of AMR in Saskatchewan, with the goal of identifying approaches that would be most effective at preventing the establishment of AMR in the province. Given the current low levels of AMR compared to other jurisdictions, such as China, Saskatchewan has a unique opportunity to be proactive in preventing the emergence of AMR. The identification of effective strategies to prevent AMR emergence is critical if we are to avoid a future in which the prevalence of AMR limits treatment options, and pushes disease rates even higher. However, limitations inherent to Saskatchewan's STI data system substantially restrict the strength of a dynamic simulation modeling approach grounded in empirical data. In fact, data-related limitations identified in the previous chapter proved to be magnified when the data were used to inform the model building process.

6.1 Introduction

Rates of gonorrhea are high in Saskatchewan compared to other provinces. Saskatchewan reported 71.7 cases per 100,000 population in 2011—more than twice the rate of the provinces of Ontario and Quebec, as well as the national rate (1). Although levels of AMR have been relatively low in the province to date (2), resistance to penicillin, tetracycline, erythromycin, and ciprofloxacin is common nationally; as a result, these antibiotics are no longer recommended for treatment in Canada. Further, resistance to ceftriaxone and cefixime, the last recommended treatment, is emerging (3). Treatment failures to oral third generation cephalosporins have been reported in Canada (4), illustrating the potential of untreatable infections in the future. New therapy modalities—such as innovative treatment approaches with currently available antibiotics, the discovery of new antibiotics, or the development of vaccines to prevent gonorrhea—are needed to avoid this potential outcome. Currently, combination therapy with ceftriaxone (250 mg IM) and azithromycin (1 g po) is the recommended first line treatment for uncomplicated gonorrhea in Saskatchewan (5). This dual therapy is administered both to delay the emergence of resistance to cephalosporins in *Neisseria gonorrhoeae* and to treat for concomitant chlamydia infection (6). At present, resistance to cephalosporins has not been observed in Saskatchewan (2).

Better understanding of why Saskatchewan experiences such high rates of infection is needed to reduce the impact of gonorrhea in the province. To date, there have been few published epidemiologic studies of gonorrhea in Saskatchewan (7,8), and none have offered an explanation for the province's inordinately high rates despite low levels of AMR. The previous chapter examined the utility of enhancing traditional epidemiologic methods with SNA to advance effective disease control approaches in the province. This chapter explores simulation modeling as a potential approach for improving understanding of the complexities of gonorrhea transmission in the context of emerging AMR.

Simulation modeling offers a powerful tool for the application of health data to policy decisions. For example, models can be used to predict emergence or reemergence of antimicrobial resistance, compare and contrast the impact of different contact tracing strategies on disease prevalence, evaluate the effectiveness of screening programs, identify the most cost-effective disease control strategies, and more. Modeling offers a unique opportunity to generate and test

hypotheses related to identifying the best possible strategies for the control of gonorrhea—information that is urgently needed in a province where rates remain substantially higher than for the rest of the country. However, a review of the literature reveals relatively few published studies over the past 15 years that apply simulation modeling to problems related to gonorrhea in the developed world. Further, only two of these papers focus on AMR gonorrhea (9,10)—one that I have coauthored.

In light of the remarkably high rates of infection in the province, it would be prudent to be proactive in preparing for the eventual emergence of AMR in Saskatchewan. Given national trends, it is plausible that AMR could complicate gonorrhea control locally in the near future. Compounding this risk, international travel and high rates of immigration to Saskatchewan (11) also increase the likelihood of introduction of AMR infections. To this end, the objective of this chapter was to use simulation modeling to explore potential outcomes related to the introduction of AMR into a population where resistance to cephalosporins is not currently observed (2). Ten years of data from the Regina Qu'Appelle Health Region's notifiable STI files provide empirical evidence to inform the structure and calibrate the model.

6.2 Methods

6.2.1 Model

The research presented here used a previously published compartmental model designed to explore scenarios related to the effects of AMR on gonorrhea prevalence under various treatment options. The model was originally published in 2011 (9), and was later modified by our research group to better represent infection transmission dynamics in discrete populations (10). Detailed descriptions of the original model and how it was initially modified are available in the publications referenced. Additional changes to the structure and to model parameters for this analysis are described below.

The model modified for the work presented here was originally created in Vensim DSS (12)—a popular numerical software for system dynamics models (constituting ordinary differential equations). The same software was used for the additional modifications and analyses described. The model was numerically integrated using the Euler method with a time-step of 0.0078125. The model uses a susceptible-infectious-susceptible structure, because gonorrhea does not result

in long term immunity, and individuals become susceptible to reinfection once they have recovered. In the original model, several compartments allowed for individuals to be infected with one of four types of infection: infection susceptible to treatment, infection resistant to drug A, infection resistant to drug B, and infection resistant to both drugs. The original model was risk-stratified, with 97.4% of the population classified as low risk, 2.3% as intermediate risk, and the rest as high risk. The total closed population numbered 1 million, and did not include demographic characteristics such as age or gender. The duration of infectiousness was 42 days and the chance of developing resistance upon treatment was 10^{-6}. Proportional mixing among risk groups, with homogenous mixing within risk groups, was represented using a mixing matrix (see Appendix 6.A for equations). All parameters and structural features, except those discussed below, were reproduced exactly as reported in the original model.

6.2.2 Sample data source

Ten years of data from the notifiable STI files of Regina Qu'Appelle Health Region (2003-2012) were used to inform the structure and parameters used in this study. The dataset is described in detail in our previously published manuscript (8) and in Chapter 5 of this dissertation. Briefly, every positive gonorrhea case recorded in RQHR over this time period was included. The RQHR files contained demographic information, including name, health services number (HSN), age, date of birth, and address; event-related information including diagnosing facility, laboratory tests reported, and type and date of treatment; and, risk factor information including sexual history, drug and alcohol use, and number of partners. Information on sexual contacts and their follow-up was also recorded. All contacts who presented and had a laboratory-confirmed infection were also included in the extracted list of gonorrhea cases.

These data were used to build maps of the sexual network for each year, and SNA measures including network density, component size, and degree were calculated for each year. Density measures the total number of connections in a network divided by the total possible number of connections (13); a very dense network is one in which many nodes are connected to one another. A component is a subgroup in a network in which all nodes are connected by at least one tie (13), and component size refers to the total number of nodes in the given component. Degree indicates the total number of connections a node has (13); in this case, degree represents

the number of sexual contacts reported, and is based on naming a contact, and/or being named by someone else.

6.2.3 Modifications

Several modifications to the previously published model were made before running any scenarios. The modifications were made mainly to enhance the model's representativeness in characterizing gonorrhea transmission in populations of interest. Specifically, the modified model was designed to better represent the population of STI clinic attendees in the Regina Qu'Appelle Health Region, using empirical data gathered through our previous studies among this population (8).

RQHR records an average of 100 cases of gonorrhea and 1000 cases of chlamydia per year. A population size of 11,000 was used, to approximate the number of STI notifications filed in RQHR for gonorrhea and chlamydia over the 10-year period from which the data were gathered. The model population was stratified into the two risk categories—high and intermediate—that plausibly make up most of the STI notifications (and their contacts) over the study period. Degree (calculated by SNA) values for cases were used to determine the appropriate proportions represented by each of these categories, with degree 2 or below representing intermediate risk and degree 3 or above representing high risk.

Values for contact rates were also modified from the original model, based on the cases' degree values from the RQHR data. The mixing matrix was adapted to account for only two risk groups, using values based on the SNA of the RQHR data. The proportion of each population stratum that received treatment was also abstracted from the RQHR data. Lastly, the original model used a treatment delay of one year. A treatment delay of 3 months was used here, to better reflect the various factors affecting when a person might present for treatment. For example, symptomatic males would likely present for treatment soon after symptom onset, while in other cases treatment might result from tracing of asymptomatic contacts, resulting in a longer time from infection to treatment.

Before running any scenarios, the mixing matrix was balanced so that the number of contacts per unit time occurring from the intermediate risk population with those in the high risk population equaled the number of contacts per unit time occurring from the high risk population with those

in the intermediate risk population. That is, (population proportion of intermediate risk individuals * intermediate risk group contact rate * proportion of intermediate cases' contacts with high risk individuals) was equal to (population proportion of high risk individuals * high risk contact rate * the proportion of high risk cases' contacts with intermediate risk individuals).

Lastly, the original model allowed for combination therapy with two antibiotics; in this study only one drug was considered.

6.2.4 Parameter values

Based on the results of the SNA, the population was structured such that 90% were classified as intermediate risk and 10% high risk individuals. In any given year, the proportion of infected individuals the high risk group to receive treatment was 0.82, and the proportion of infected individuals in the intermediate risk group to receive treatment was 0.59. Also based on the SNA results, using degree values for the index cases, the contact rate for the intermediate risk group was 1.19 per year; for the high risk group, it was 3.56 per year. The connections between individuals revealed by the SNA indicated that for high risk individuals, 97.1% of contacts were with intermediate risk individuals, and 2.9% with other high risk individuals. For intermediate risk individuals, 95.5% of contacts were with other intermediate risk individuals and 4.5% were with high risk individuals.

Based on the raw data, not only was the matrix unbalanced, but the proportion of contacts that are high risk was *higher* among the intermediate risk cases than among the high risk cases. It is highly improbable that this reflects the true nature of pairing across risk groups (e.g., it is unlikely that intermediate risk cases are more likely to pair with high risk contacts than are high risk cases), and indicates an inconsistency in the original data. In reality, the fraction of high-risk cases who mixed with high-risk contacts is probably much greater. This underestimate of high risk-high risk pairings likely results from censoring at the edges of the network. Because the data used for the SNA generally only included first generation contacts, most of the components identified were star shaped. This means that information about individuals at the edges of such stars was necessarily censored. Contacts were assigned risk categories according to the results of the SNA. Most of these nodes, therefore, were assigned to the intermediate risk category, but were connected to a high risk case. To account for this misclassification of contacts, correction factors were applied to move contacts from the intermediate risk group to the high risk group in

the mixing matrix only. To balance the matrix, the proportion of high risk contacts was increased by a factor of two for intermediate risk cases, and by a factor of 25 for high risk cases. The corrected mixing matrix was structured such that for high risk individuals, 73% of contacts were with other high risk individuals, and 27% were with intermediate risk individuals. For intermediate risk individuals, 9% of contacts were with high risk individuals, and 91% were with other intermediate risk individuals. (Table 6.1)

Additionally, a multiplier of seven was applied to the force of infection, to enable the infection to become established in the population at a level similar to what has been reported in empirical studies.

Table 6.1 Dynamic model to investigate antimicrobial resistance scenarios in Saskatchewan: parameters and baseline values

Parameter	Symbol	Baseline value	
Probability of developing de novo resistance on therapy	r_A, r_B	0.000001	
Natural recovery rate (1/year)	v	8.67	
		High risk	**Intermediate Risk**
Population size	N_i	1100	9900
Total annual partnerships	c_i	3.56	1.19
Proportion of sexual partnerships*			
High risk	p_{2i}	0.73	0.27
Intermediate risk	p_{1i}	0.09	0.91
Baseline daily rate of treatment	t_{Ai}, t_{Bi}, tA_{Bi}	0.011	0.011
Proportion treated		0.82	0.59

*Corrected as explained in text.

6.2.5 Scenarios

The first scenario established the baseline steady-state prevalence of infection, which resulted from the parameters abstracted from the RQHR data. It used a treatment delay of 3 months and did not allow for AMR.

The second set of scenarios examined the effect of varying treatment delays, both in the presence of resistance, and without resistance. In the scenarios with AMR, the initial level of resistance was set at 1% of infections across both risk strata. Treatment delays explored included 1 year (as

structured in the original model), 6 months, 3 months, 2 months, six weeks, and 1 month to treatment.

Finally, a set of scenarios was constructed to evaluate the effect of introducing different levels of resistance into the population under different treatment scenarios. These scenarios involved trying to determine a "tipping point" for the frequency of resistance introduced to the population necessary to affect the steady-state prevalence of infection. These scenarios used a 3 month treatment delay, and involved introducing varying levels of resistant infections at the initial time-step of the model.

6.3 Sensitivity analyses

To explore the sensitivity of the model to other changes in selected parameters, scenarios were run to examine the effects of increasing population size, and treating 100% of each risk group as opposed to the baseline treatment proportions abstracted from the RQHR data. These analyses were performed using the baseline conditions with no AMR and a three month treatment delay. Increasing the number of individuals in the model by up to a factor of 1000 revealed that the model was not sensitive to changes in population size. The model was sensitive to changing the proportion of the infected population to receive treatment in a given year, however. When the treatment proportion was modeled at 0.5 in each risk stratum, the resultant steady-state prevalence was roughly 2,000 per 100,000 higher than the baseline. In contrast, when the entire population was treated, the steady-state prevalence was about 2,500 per 100,000 lower than the baseline.

6.4 Results

6.4.1 Baseline scenario

In the baseline scenario, after an initial decline, the steady-state prevalence of 9.9% was reached within roughly 16 months (Figure 6.1).

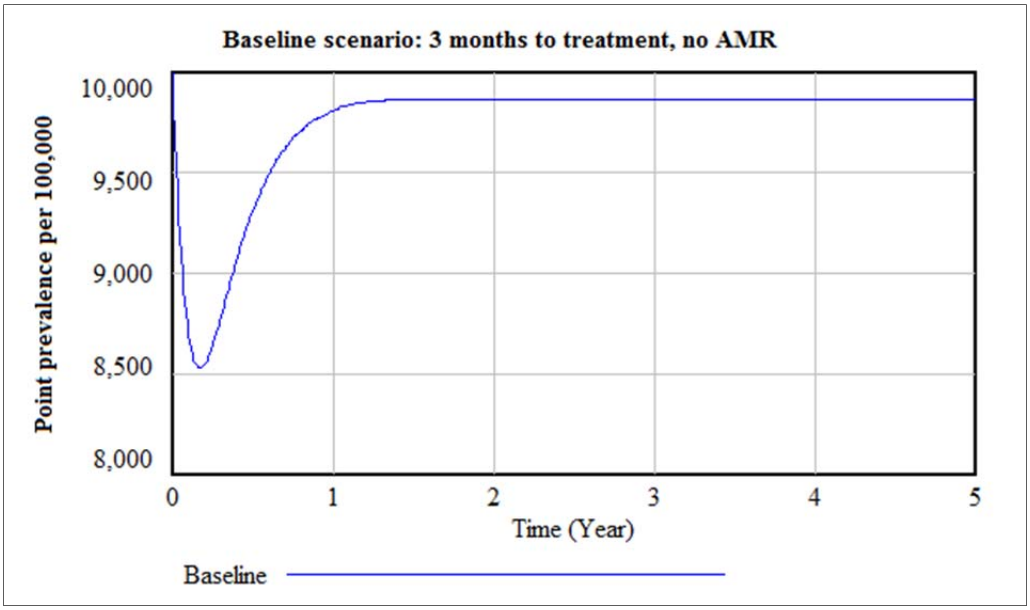

Figure 6.1 Baseline scenario with no AMR: Steady-state prevalence is 9.9%

6.4.2 Treatment delays without AMR

Varying the length of delay to treatment without AMR resulted in different levels of steady-state prevalence (Figure 6.2). The longer the delay until treatment, the higher the steady-state prevalence of the system, and the more quickly it was reached. With a one year treatment delay, the steady-state prevalence was 16.5%, and a 6 month delay resulted in a steady-state prevalence of 14.5%. The baseline (3 month treatment delay) resulted in a steady-state prevalence of 9.9%. When the treatment delay was lowered to 2 months, the resultant steady-state prevalence was 6.9%. A six week treatment delay resulted in a steady state prevalence of only 3.4%, while treating within one month resulted in the rapid elimination of disease from the population.

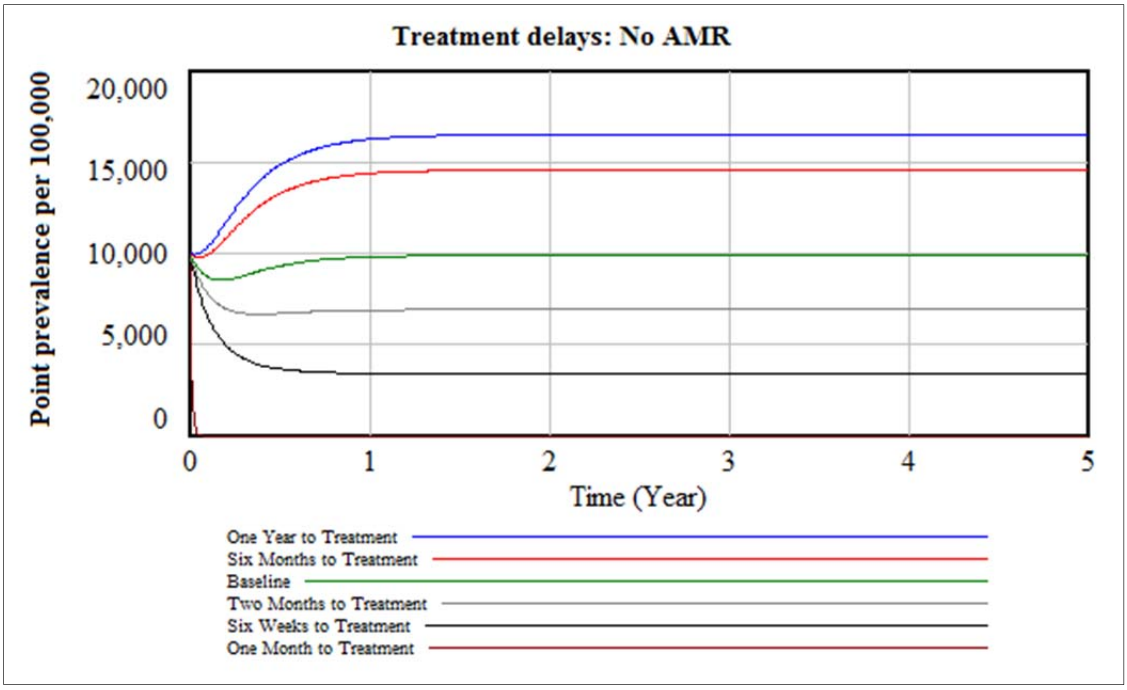

Figure 6.2 Without AMR, longer treatment delays result in higher steady-state prevalence

6.4.3 Treatment delays with AMR

Varying the length of delay to treatment when AMR is initially included (in 1% of infections) gives notably different results. In all cases, the steady-state prevalence was 19.8%, but the time to reach this level varied (Figure 6.3). The longest treatment delay (1 year) resulted in the ultimate steady-state prevalence being reached after roughly 10 years. In contrast, with a treatment delay of just one month, the steady-state prevalence was reached in under two-and-a-half years. Additionally, the results indicate that treatment in two months or less affords an initial sharp decline in prevalence, followed by a rapid rebound effect. This effect was not seen with longer treatment delays. In all of these scenarios, it is the resistant strains that were responsible for maintaining the steady-state prevalence.

6.4.4 Tipping points for AMR

The results of the last scenario are shown in Figure 6.4. Including just one resistant infection among the high risk group resulted in a steady-state prevalence of 19.8% within 4 years. Starting the model with higher levels of resistance among the high risk group (e.g., more than one individual with resistant infection) resulted in the same steady-state prevalence being reached,

but in a shorter amount of time. In contrast, it required 11 AMR initial infections among the intermediate risk group to tip the steady-state prevalence to this same level (19.8%). In these scenarios, resistant infections were largely responsible for the steady-state prevalence. Any fewer than 11 resulted in the same outcome as the baseline scenario—AMR does not become established, and resultant prevalence is maintained by non-resistant infections. As well, when AMR was initially included in the intermediate risk group, it took slightly longer to level off at this higher level as compared to when AMR occurred in the high risk group.

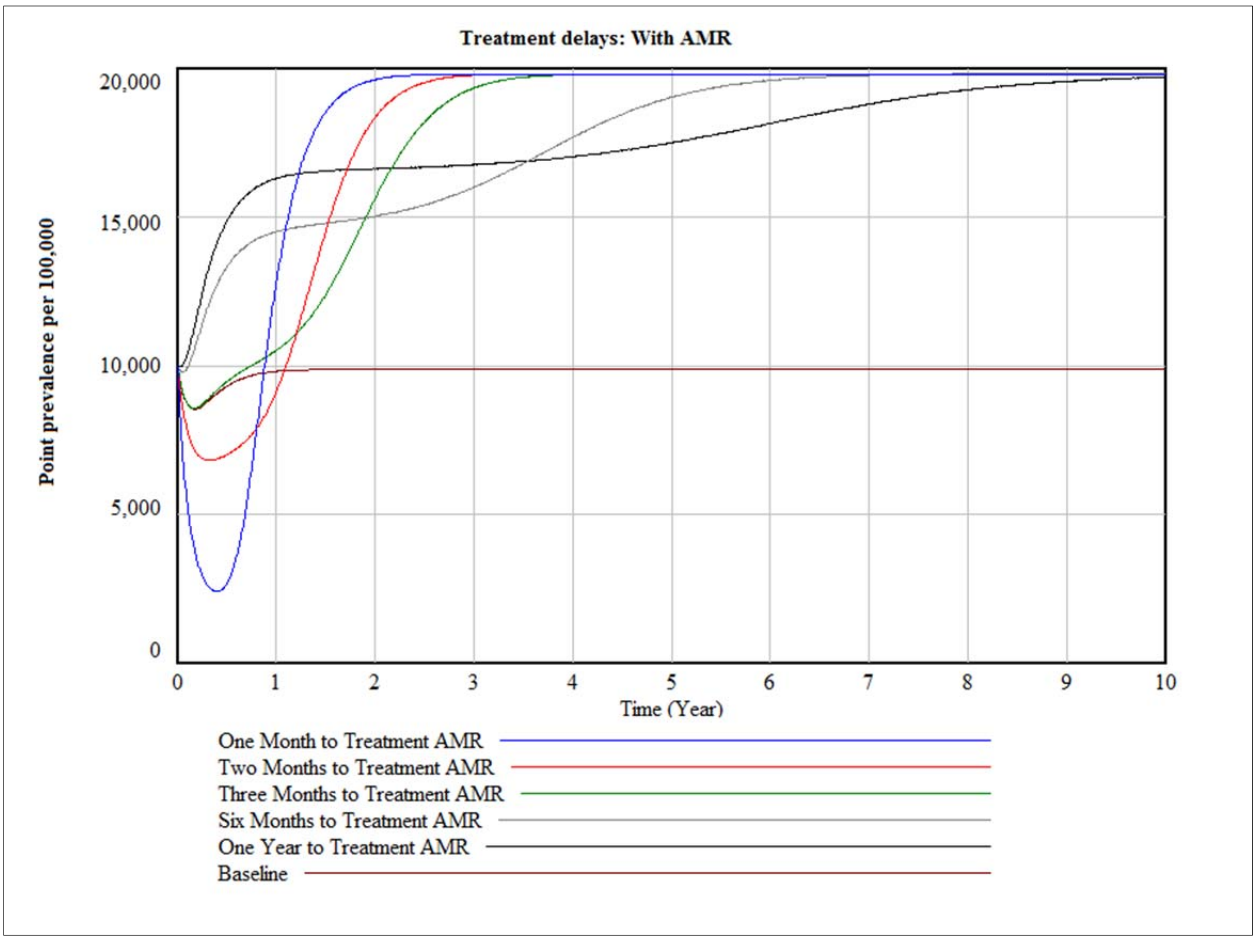

Figure 6.3 In the presence of AMR, faster treatment results in faster establishment of steady-state prevalence of infection

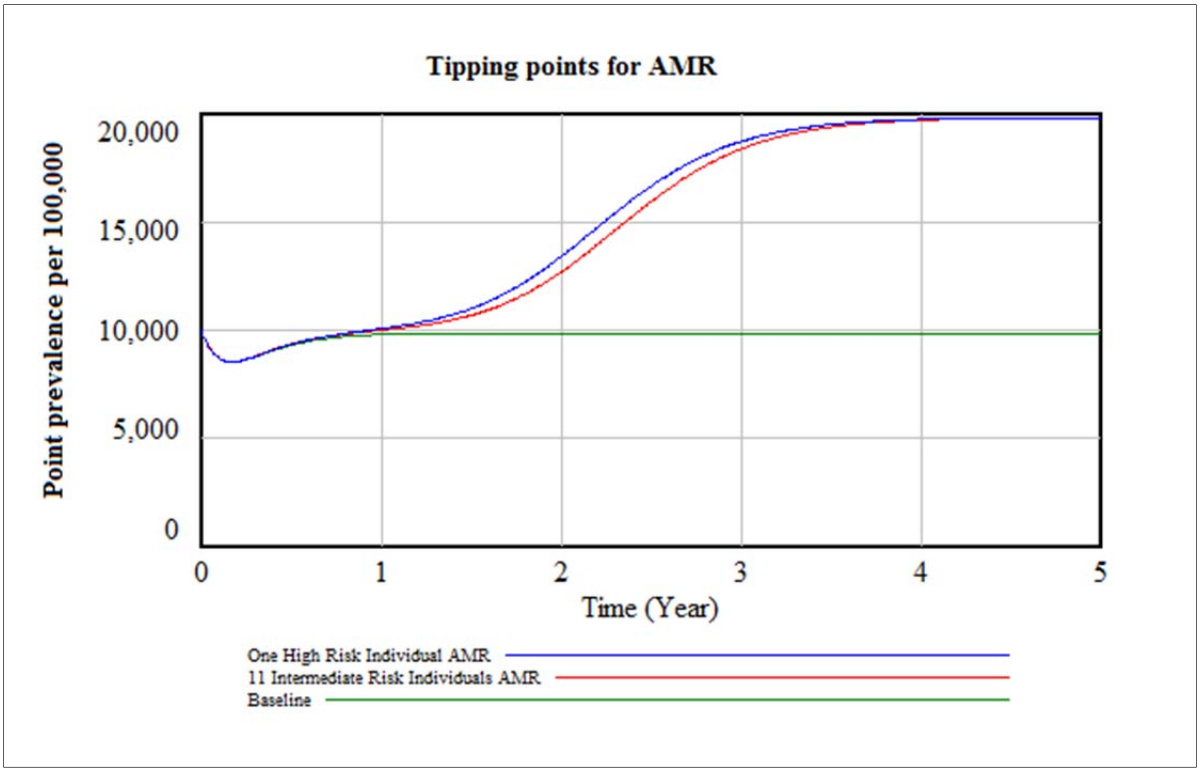

Figure 6.4 Fewer resistant infections are required—and the effect is faster—if resistance is modeled among the high risk versus the intermediate risk group

6.5 Discussion

The combination of Saskatchewan's high rates of gonorrhea, coupled with the threat of untreatable infection, makes it crucial that effective disease control policies are in place. The present high rates indicate that improved understanding of gonorrhea transmission dynamics in the province is urgently needed to inform the development of effective policies, and that the current approach could be improved. The very real potential for the development of resistance to currently-recommended treatments indicates the importance of being proactive to mitigate the possible effects. There have been relatively few recent studies using dynamic simulation modeling to explore scenarios related to gonorrhea transmission and control in the developed world. Those that have been published in the last 15 years have explored topics including treatment approaches (9,10,14), diagnostic testing (15,16), financial aspects of disease control (14,16–19), and screening approaches (14,17–19). Only two have focused on AMR—one published by our research group (9,10). This is the first study to attempt to model scenarios related to the development of AMR in Saskatchewan, using empirical data.

The baseline steady-state prevalence of 9.9% is similar to the prevalence of gonorrhea reported among core groups in previous studies (20,21). As well, a prevalence of 10% was used for the high risk group in the original model (9,10), indicating this is in line with expected values for the STI clinic population.

It was not surprising that increasingly longer treatment delays—in the absence of AMR—resulted in increasingly higher levels of steady-state prevalence. Notably, a reduction of the time to treatment from three months (baseline) to 2 months reduced the steady-state prevalence by roughly one-third, while a reduction from 2 months to 6 weeks reduced it by about 50%. The difference between a treatment delay of one year and 6 months only reduces steady state prevalence by 12%. Within the limitations of the parameter values applied (see below), these results suggest that treating within 6 weeks could be key, which has important implications for policies related to empirical treatment as well as contact tracing approaches. In jurisdictions where identification and treatment of contacts is known to take several weeks, expedited partner therapy (EPT) could be a reasonable choice given these findings.

The opposite effect was shown by varying treatment delays in the presence of AMR. In this case, the faster individuals are treated, the faster resistant strains are able to take hold in the population, resulting in higher steady-state prevalence. In a population with AMR, in the absence of a point of care test to enable the delivery of targeted, effective treatment, a delayed time to treatment with a single antibiotic appeared to slow the rise to an eventual steady-state prevalence of 19.8%. This underscores the need to develop rapid point-of-care tests for antimicrobial susceptibility; being able to deliver appropriate, effective treatment at the initial visit is fundamental to controlling disease.

The results of the exploration of the "tipping points" for AMR taking hold in the population were interesting. Starting the model with just one high risk individual with a resistant strain was enough to push the steady-state prevalence to 19.8% in 4 years, fueled by AMR infections. In contrast, it required 11 times as many individuals with AMR infection in the intermediate risk group to have a similar effect. This implies that the high risk group—while substantially smaller than the intermediate risk group—is driving the spread of infection in the population. The high risk group's demonstrated influence on infection transmission is in line with core group theory, which indicates that a small group of individuals with high risk behaviors play a large role in

maintaining STI epidemics (22). These results also demonstrate the potential for a very small numbers of individuals with resistant infection to tip the balance to a higher overall prevalence of infection, quite rapidly.

Many of the most important implications of this work come from the model building process itself. The availability of 10 years of STI data from RQHR enabled elements observed among this sample population to be incorporated in the model. As well, the results of SNA of this data allowed for the use of parameters (such as contact rates, and mixing preferences) that were grounded in empirical data. However, the considerable limitations of the data became apparent at the start of the model building process.

The biggest limitation of using the RQHR data was the misclassification of high risk contacts as intermediate risk. This misclassification, as discussed earlier, results from the way in which the data on contacts was collected. Because contacts beyond those reported by the index case (e.g., the contacts' contacts) were generally not identified, this necessarily limited the ability of the SNA to accurately represent the extent of the network, and, therefore, the risk group of many contacts. This is in part related to the lack of a centralized system for STI data collection and storage in Saskatchewan (see discussion Chapter 5), which greatly restricts the extent of the network that can be uncovered. This first-generation-only contact tracing results in a social network map where most of the larger components are star shaped. Individuals on the edges of such stars are censored, meaning that the degree measurement calculated from the data—and used to abstract risk groups, here—is lower than it likely is in reality. As a result of these star-shaped components, many high risk individuals (the centers of the stars, with high degree measures), are connected to individuals who are classified as intermediate risk, based on this censoring. Because of this, the raw data were providing highly inconsistent contacts per unit time when viewed from the point of view of the intermediate risk population mixing with the high risk population and from the point of view of the high risk population mixing with the intermediate risk population. An adjustment to the raw values was clearly needed to correct for this. The correction approach used was chosen to address the fact that the contacts of high risk cases are *disproportionately* affected by censoring, and needed to be substantially increased. The correction factors applied were chosen to address this differential effect of censoring and establish a more realistic mixing matrix. It is interesting to note that this considerable limitation

inherent in the dataset likely would have gone unnoticed had we not attempted to use the SNA data to inform our model.

Underreporting of contact rates was another limitation, and was hypothesized to be the reason a multiplier was needed to provoke the establishment of infection in the population. This underreporting has a few likely causes. First, the degree values from the SNA are calculated based upon the number of unique partnerships reported, and do not account for multiple partnering with the same contact, nor for the effect of concurrent partnerships on disease transmission. Second, contact tracing is generally known to have inherent limitations to uncovering the complete network, based on a wide variety of issues (23); additional factors possibly limiting the effectiveness of contact tracing in RQHR were discussed in the previous chapter. The need to implement a multiplier might also relate to additional inconsistencies in the mixing matrix, beyond the misclassification we attempted to account for. In light of these limitations, the need to use a multiplier on the force of infection was not surprising. This adjusted force of infection accounts for the underreporting and other issues discussed above, in a relatively simplified manner, and speaks to the inability of contact tracing data alone to capture adequate information about disease transmission dynamics.

Another limitation was the lack of available data on the low risk population in RQHR. It is plausible that the majority of truly "low risk" individuals rarely, or never, contract an STI. Therefore, the notifiable STI files for RQHR likely contain very few such low risk individuals. This assumption guided the decision to divide the population into two, rather than three, risk strata. However, by limiting the model to intermediate/high risk individuals only, it was not possible to investigate broader implications of the emergence of AMR in the population as a whole. Data on the proportion of STI contacts who are low risk—along with information about their specific risk behaviors, and connections with other risk groups—would allow for a more complete analysis, including the entire (sexually active) population.

In spite of being grounded in empirical data, the model presented here is highly stylized. However, by using dynamic modeling to explore the potential effects of AMR in a naïve population, this work provides a starting point for discussion and further consideration of the potential effects of the emergence of AMR gonococcal infection in Saskatchewan. There are substantial public health implications related to the establishment of AMR in *N. gonorrhoeae*

circulating in the province, which could ultimately compromise the effectiveness of current contact tracing and treatment policies. Additional questions of interest for future exploration could include the modeling of different contact tracing approaches and/or coupling molecular strain typing data with traditional contact tracing data. Using the currently available RQHR data to inform an agent-based model could serve to expand upon the work presented here. As well, this work illustrates the potential need to reconsider the way STI data are collected and stored in Saskatchewan; under the current system, the ability of otherwise powerful epidemiologic techniques to contribute to disease control approaches is considerably hampered.

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Appendix 6.A: Original model equations

$$\frac{dS_i}{dt} = -S_i c_i \left(p_{i1} \frac{I_{01}+I_{A1}+I_{B1}+I_{AB1}}{N_1} + p_{i2} \frac{I_{02}+I_{A2}+I_{B2}+I_{AB2}}{N_2} + p_{i3} \frac{I_{03}+I_{A3}+I_{B3}+I_{AB3}}{N_3}\right) + v(I_{0i} + I_{Ai} + I_{Bi} + I_{ABi}) + I_{0i}[t_{Ai}(1-r_A) + t_{Bi}(1-r_B) + t_{Abi}(1-r_A r_B)] + I_{Ai}t_{Bi}(1-r_B) + I_{Bi}t_{Ai}(1-r_A) + I_{Ai}t_{ABi}(1-r_B) + I_{Bi}t_{ABi}(1-r_A) \quad (6.1)$$

$$\frac{dI_{0i}}{dt} = S_i c_i \left(p_{i1} \frac{I_{01}}{N_1} + p_{i2} \frac{I_{02}}{N_2} + p_{i3} \frac{I_{03}}{N_3}\right) - v I_{0i} - I_{0i}(t_{Ai} + t_{Bi} + t_{ABi}) \quad (6.2)$$

$$\frac{dI_{Ai}}{dt} = S_i c_i \left(p_{i1} \frac{I_{A1}}{N_1} + p_{i2} \frac{I_{A2}}{N_2} + p_{i3} \frac{I_{A3}}{N_3}\right) - v I_{Ai} - t_{Ai} I_{0i} r_A - I_{Ai}(t_{Bi} + t_{ABi}) \quad (6.3)$$

$$\frac{dI_{Bi}}{dt} = S_i c_i \left(p_{i1} \frac{I_{B1}}{N_1} + p_{i2} \frac{I_{B2}}{N_2} + p_{i3} \frac{I_{B3}}{N_3}\right) - v I_{Bi} + t_{Bi} I_{0i} r_B - I_{Bi}(t_{Ai} + t_{ABi}) \quad (6.4)$$

$$\frac{dI_{ABi}}{dt} = S_i c_i \left(p_{i1} \frac{I_{AB1}}{N_1} + p_{i2} \frac{I_{AB2}}{N_2} + p_{i3} \frac{I_{AB3}}{N_3}\right) - v I_{ABi} + t_{ABi} I_{0i} r_{AB} + I_{Ai}(t_{Bi} + t_{ABi}) r_B + I_{Bi}(t_{Ai} + t_{ABi}) r_A \quad (6.5)$$

where S_i and I_i are the number of susceptible and infected individuals in each risk group *i.* Subscripts attached to *I* indicate infection with strains susceptible (*0*) or resistant to one or more strains (*A, B, AB*). *j* is used to denote risk groups other than *i*. (Note that the modified model includes only two risk groups and examines scenarios using only one drug.)

CHAPTER 7: CONCLUSIONS

High rates of infection, coupled with growing AMR, make *Neisseria gonorrhoeae* a substantial public health threat. Understanding the influence of local epidemiology and socio-demographic factors on transmission dynamics is integral to developing successful disease control policies. A wide variety of epidemiologic tools are available to public health professionals. For successful approaches to disease control to be identified and implemented, it is important that the relative strengths and weaknesses of available tools be understood. Different disease settings, and varying levels of data quality, strongly influence the power of a particular tool in any given situation. Novel approaches to disease control, such as SNA or dynamic simulation modeling, can theoretically enhance traditional approaches. The objectives of the work presented here were to contribute to the current understanding of effective control of gonorrhea, to better understand factors related to the development and persistence of AMR, and to evaluate the effect of local epidemiology of disease in contrasting geographic regions, coupled with quality of available data, on the effectiveness of different analytical tools.

7.1 Summary of findings

Traditional approaches grounded in biostatistical analysis remain the cornerstone of epidemiologic studies of infectious diseases like gonorrhea. Chapters two through four of this dissertation illustrate the power of biostatistical approaches to identifying potential leverage points to control disease spread and the development of AMR. Chapters five and six consider the contribution of novel epidemiologic tools—SNA and dynamic simulation modeling.

The first two of these chapters draw upon data from Shanghai, China—a region with very high rates of infection and AMR. The analysis presented in Chapter 2 shows that it is possible to identify behaviours and client attributes associated with AMR infection using robust statistical methods, even where rates of AMR are extremely high. In the absence of point of care testing for antimicrobial susceptibility, which would enable the delivery of timely, effective treatment, such information could potentially be used to better tailor treatment approaches using risk factor profiles. The study presented in Chapter 3 demonstrates that patient behaviours and socio-demographic characteristics can also be used to predict both safe-sex practices and the likelihood of bringing a partner to testing/treatment after a positive gonorrhea diagnosis. This work shows that information that can be solicited in a clinical visit may be useful for helping clinicians tailor

the most appropriate counseling and/or follow up of a given case—especially important in high-prevalence regions.

The remaining chapters draw upon data from Saskatchewan, a setting where disease rates are high, but AMR is not currently a large concern. Chapter 4 presents further evidence that statistical approaches can reveal associations between socio-demographic characteristics and behavior with outcomes of interest for disease control—in this case risk for repeat gonorrhea or being coinfected with chlamydia and gonorrhea. Similar to the findings in Chapter 3, these results could be useful in helping clinicians tailor approaches to treatment and counseling based on factors that can be elicited during a patient visit. This is of particular interest in Saskatchewan, where disease rates are high, but only two published epidemiologic studies of gonorrhea exist. Chapter 5 presents an attempt to leverage SNA to augment the analytical approach presented in Chapter 4. This study represents the first to use SNA to study gonorrhea in Saskatchewan, provides new information about the characteristics of the gonorrhea network in RQHR. However, incorporation of SNA measures into the previously-published multivariable statistical analysis did not result in any major differences in the findings of the original study. This is likely related to the inherent limitations of the dataset.

The work presented in Chapter 6 represents one of relatively few studies over the last 15 years to apply dynamic simulation modeling to questions related to gonorrhea transmission. Because rates of AMR are currently low in Saskatchewan, a proactive approach to reducing the impact of AMR infections is warranted. The model presented in this chapter builds upon previously-published compartmental models, enhancing them with empirical data from the Regina Qu'Appelle Health Region. The model is useful for provoking discussion around appropriate treatment and follow-up approaches under various scenarios in the presence of, and without AMR strains circulating. While intrinsic limitations of the data restricted the strength of the model to provide robust real-world representativeness, the results do provide the groundwork for consideration of factors related to the eventual emergence of AMR gonococcal infections in Saskatchewan. Perhaps more importantly, this work further underscores the drawbacks of the current system of collection and storage of STI data in Saskatchewan.

7.2 Limitations

That data collected in the Shanghai study had some substantial limitations, which precluded the generation of findings with definitive and broad public health applications to the control of gonorrhea. Large amounts of missing data, lack of heterogeneity in questionnaire responses, and low overall response rates likely restricted robustness of analysis. Further, because the index cases in the study population were all index males—the only females being those partners who presented—did not allow for comparison of male and female index cases in this population. Last, because the population was drawn from one STI clinic, generalizability of findings is limited.

One of the most important findings of this body of work relates to the considerable limitations of STI data routinely collected in Saskatchewan for the application of powerful techniques such as SNA and dynamic simulation modeling. While this work shows that traditional biostatisical approaches to data analysis continue to be useful in identifying associations between risk factors and outcomes, SNA and dynamic simulation modeling should offer an additional increase in analytical power. As demonstrated in other studies, such methods provide platforms to greatly enhance our understanding of the more nuanced elements of the disease system, such as the influence of the local sexual network, or the potential effect of the introduction of even small numbers of AMR infections to a population. Unfortunately, these methods rely on robust data to be exploited to their full potential; the data available in Saskatchewan proved to be far from perfect for these applications.

The fragmented system of data collection and storage, related to jurisdictional boundaries of the province's Regional Health Authorities, and the First Nations and Inuit Health Branch, vastly limited the extent of the sexual network that could be examined. This in turn limited the utility of the SNA-derived data for informing the AMR model. It was not possible to uncover geographic bridging, for example, since the data available for analysis came from just one health region. Without a centralized system of data storage for STIs, the true potential of SNA to contribute to better understanding of gonorrhea transmission in Saskatchewan will remain limited. The strength of these techniques could be greatly enhanced—and the resultant impact on disease rates considerable—if Saskatchewan were to adopt a centralized approach to STI control.

7.3 Future work

While the limitations presented by the data restricted the power of SNA and dynamic simulation modeling to substantially enhance traditional biostatisical methods, the work presented here nevertheless generated some interesting findings. For one, this body of work reinforces that the power of a tool is highly dependent upon the availability of appropriate data. The epidemiology of gonorrhea in Saskatchewan indicates that improved understanding of disease transmission dynamics is needed to enable policy makers to re-evaluate the current approaches to control; however, the available data substantially hinder the ability to apply powerful tools such as SNA and dynamic modeling. These results challenge the status quo for case management of gonorrhea, as well provincial policies and procedures related to sample collection, analysis, and data storage in Saskatchewan. Put simply, a large amount of personal health information related to STIs is being collected and stored in Saskatchewan; the applicability of such data to approaches that could considerably improve disease control tactics, however, is considerably hampered by the system itself. The only current use of this data is to locate and treat cases and contacts—with persistently high disease rates, it may be time to consider alternate policies. A standard policy of taking samples for culture, and including both strain typing and antimicrobial susceptibility testing on these samples, would improve the potential application of these tools to controlling STIs in the province. Point of care testing (for both infection and antimicrobial susceptibility) would greatly contribute to disease control efforts, as well as help stave off the emergence of AMR infections in currently naïve settings like Saskatchewan. As well, EPT in place of—or in addition to—contact tracing might also warrant consideration as a policy option.

Based on the findings presented here, there are several possible directions for future work:

7.3.1 Epidemiologic predictors of AMR

Because of the growing threat of AMR, better understanding of the epidemiologic risk factors for AMR infection is urgently needed. To date, there have been only a small number of published studies that examine associations between socio-demographic characteristics and AMR infection. Future work to identify such associations is needed to better understand the generalizability of the findings of the studies to date. Further, rigorous statistical analysis should be a standard for such investigations, in order to support development of effective policies to combat AMR. A uniform approach to collecting a minimum amount of epidemiologic data on STI cases would

increase the potential strength of this approach to identifying socio-demographic risk factors for AMR globally. This type of information would be particularly valuable in settings where AMR infection is highly prevalent, such as Shanghai. It may also be applicable to preventing AMR from taking hold in currently naïve populations.

7.3.2 Treatment and follow up of gonorrhea in Saskatchewan

Based on Saskatchewan's persistently high prevalence of gonorrhea, evaluation of the effectiveness of current treatment and follow up approaches are warranted. Further studies in other health regions, to validate the factors identified to be related to reinfection and coinfection in RQHR, could provide the groundwork for developing alternative strategies. For example, EPT may be practical in certain situations, based on the risk factor profile of a given patient.

7.3.3 SNA for gonorrhea in Saskatchewan

As mentioned above, the current system of data collection and storage in Saskatchewan makes it challenging to use SNA to its full potential. Future work could focus on enhancing the quality of available data. For example, increasing the number of spaces available to record contacts on the notifiable STI form could potentially enhance case finding, resulting in a more complete sexual network. Additionally, a prospective study to gather samples for molecular information from positive gonorrhea cases would allow for molecular strain type information to be superimposed on sexual network maps, and the potential contribution of this information to be assessed.

7.3.4 Dynamic simulation modeling of gonorrhea where AMR rates are low

In spite of global trends, and high infection rates in general, rates of AMR gonorrhea in Saskatchewan remain remarkably low. Therefore, the province presents a unique opportunity to consider different strategies for antibiotic use and the potential for eventual emergence of AMR. For example, since penicillin resistance is quite low in the province, it may be possible to effectively use it to treat gonorrhea locally, although the antibiotic is no longer recommended nationally. Dynamic simulation modeling provides a powerful platform for investigating a question like this, and could generate valuable information to policy makers who might consider creating local treatment guidelines.

Another recommended future modeling study is to build an agent-based model to represent gonorrhea transmission in Saskatchewan, which would increase the model's ability to

incorporate and reflect real-world conditions as compared to the system dynamics model presented here. An agent-based model would provide the opportunity to model the influence of the sexual network on disease transmission, as well as allow for the effect of stochastics.

In spite of the limitations of the data discussed above, the work presented herein contributes important information related to the control of gonorrhea in two high-prevalence settings. Further, it demonstrates the feasibility of using sociodemographic characteristics to discover associations with outcomes related to AMR, sexual behavior, likelihood of partner presentation, and risk of reinfection/coinfection. The value of SNA and dynamic simulation modeling approaches in Saskatchewan is difficult to judge, due to the limitations of data appropriate for these purposes. It is likely that their contribution could be substantial, given robust data sources. Expanded studies drawing on data from multiple health regions could allow for better evaluation of the contribution of these techniques, especially SNA. This would enable the larger sexual network to be discovered, which would likely provide more realistic estimates for SNA measures. Further, if molecular strain typing became a standard procedure in the province, there would be great potential to enhance the information provided by fragmented, incomplete networks as the ones derived from the RQHR data. However, at present, this would likely be cost-prohibitive.

The manuscripts presented in this thesis serve to compare and contrast the relative utility of several epidemiologic methods, both traditional and novel, as applied to different aspects of the control of gonorrhea transmission and the development of AMR. The results of the studies show enormous potential for novel or combined approaches to the analysis of STI data. However, they also demonstrate the severe limitations encountered for certain methods in certain regions. This body of work indicates that there is no one-size-fits-all approach to best address questions related to controlling gonorrhea incidence or the emergence of AMR. Rather, careful consideration of the research question, available data, and population of interest is required to ensure that the most appropriate tools are applied to the specific problem at hand.

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Molly Trecker
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Vaccine and Infectious Disease Organization
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